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THE GROSS ANATOMY OF THE LYMPHATICS OF THE HUMAN PANCREAS*

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IN SPITE of a number of anatomic studies of the lymphatic system,[1, 2, 12, 13, 17, 19, 21, 22, 32-37] the anatomy of the human pancreatic lymphatics has received little attention. Even the most recently published treatise dealing with surgical diseases of the pancreas,[3] although describing in some detail the arterial supply and the venous drainage of the organ, gives little description of the lymphatic system. This organ is not readily adapted technically to such study because of its location and physical constitution. In view of the unfavorable results obtained in the surgical management of carcinoma of the head of the pancreas, as well as other pathologic states affecting this organ, it was believed that a detailed study of the anatomy of the pancreatic lymphatics might be of value. Accordingly, a detailed examination was made of the pancreatic lymphatics in thirty human cadavers following injection with India ink suspension. An attempt will be made to correlate these observations with the current surgical management of patients with carcinoma of the pancreas.

MATERIAL AND METHOD

Pancreatic specimens from twelve adults, fifteen stillborns, and three infants were examined. The twelve adults, six of whom were white and six Negro, ranged in age from 19 to 80 years; eight were men and four women. The interval of time between death and examination ranged from two hours to seven days. All but two, however, were examined within twenty-four hours. The fifteen stillborns, two of which were white and thirteen Negro, ranged in crown-rump measurement from 28 to 35 cm. There were six males and nine females. The interval of time between birth and examination ranged from three to twenty-seven days. The ages of the three infants were 1, 2, and

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10 days, respectively; there were two Negro girls and one white boy. Two had been dead twenty-four hours and one seventy-two hours when examined.

A simple, unfiltered mixture of Higgins waterproof India ink and distilled water in dilution of 1:3 and a cartridge syringe fitted with a 27 gauge needle were employed. Commercially obtained cartridges of procaine solution were emptied by removal of the rubber stopper from one end, substitution of the India ink solution, and replacement of the stopper.

A definite plan of preparation and examination of specimens was followed. The abdomen was opened widely, the pancreas exposed through an opening in the gastrocolic omentum, and the stomach gently turned upward so that the lesser curvature pointed inferiorly. With the needle in the glandular substance of the pancreas, a small amount of the dye was quickly injected. Gentle massage was employed in all directions from the point of injection with the smooth, rounded, closed end of one of the glass containers in which the needles were packed. Particular care was taken to avoid vigorous or prolonged massage of the fetal pancreas, since maceration, with subsequent liquefaction of the glandular tissue, would result. Once the solution entered the lymphatic plexus and a lymph vessel became partially filled, the dye was easily pushed along the individual channel to its termination in a node by gently touching the vessel behind the dye with the tip of a blunt probe such as is used in gross anatomy dissection.

The injection was carried along the channels only to the first-echelon nodes. The filled channels and nodes were thoroughly examined with the aid of a binocular prism loupe prior to removal of the specimen from the body. Then, the en bloc specimen (including stomach, duodenum, pancreas, spleen, transverse colon, mesocolon, mesentery, hepatoduodenal ligament containing the root structures of the liver, aorta, vena cava, and adjacent posterior parietes from the ligament of Treitz up to the diaphragm) was removed. Areas which had been less accessible before removal were thoroughly examined, and dissection, if necessary, was accomplished with the aid of a small, sharp probe and small scissors. These observations were recorded on prepared anatomic sketches, the stomach and duodenum were inflated with air, an identifying number tag was attached, and the entire specimen was placed in a 10 per cent solution of formalin. Following fixation, questionable areas were examined microscopically, at which time additional minute dissection was undertaken and tissues for microscopic section were obtained.

Since it is practically impossible to obtain complete filling in any one specimen, especially in the fetal pancreas, it was deemed preferable to make, at most, two injections and summarize results from a composite of many specimens. This applied not only to the immediate results, but also to the results following clearing, since large amounts of the dye within the pancreas completely obscured filled channels in the cleared specimen as well. A greater number of injections could, of course, be made in the adult specimens, but

here also the same principle applied. The clearing technique was not applied to any of the adult specimens as it was thought that this would provide no additional information in such cases.

In a number of the specimens, multiple injections were made into the adjacent duodenal wall, and in many, injections were made into the head of the pancreas as closely as possible to the adjacent duodenum. This was done in an attempt to demonstrate connections between the lymphatics of the pancreas and duodenum if such existed. Duodenal injections were made into both the subserosal, submucosal, and mucosal layers.

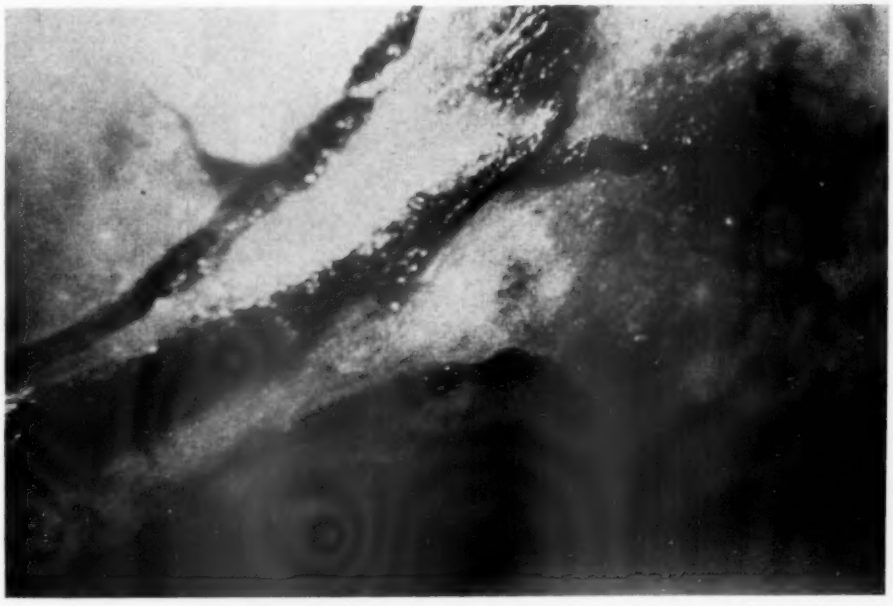

Fig. 1.—Dye-filled lymph vessels (×225; reduced ⅓).

It is often extremely difficult to distinguish between a dye-filled lymphatic vessel and a small vein in which dye has entered. Observation under the dissecting microscope will prove the existence of a true vessel as distinguished from perivascular or perilobular spaces into which dye may have entered.[21] That dye does at times enter other tubular structures and that the structure filled must be positively identified are exemplified in one specimen in which there was complete filling of the ductal system of the fetal pancreas. In this study, the most frequent source of doubt in this regard arose in relation to the question of communicating channels between duodenum and pancreas. In each such instance, where a filled vessel was found to be common to these organs, microscopic sections of the vessel were taken and stained by both the hematoxylin-eosin and the van Gieson methods. Filled channels in other areas presented less difficulty in identification, since one or more of the distinguishing criteria were commonly present. The most trustworthy of such criteria was the ability to trace the dye-filled lymphatic vessel to a lymph node containing the dye. In addition, the beaded appearance of the filled

lymphatic vessel, when viewed under the dissecting microscope, occasioned by its frequent valves, and the previously mentioned characteristic manner in which the dye progressed along the vessel, aid in identification for the practiced observer. Microscopic sections, of course, provide additional assurance in identification (Figs. 1 through 4).

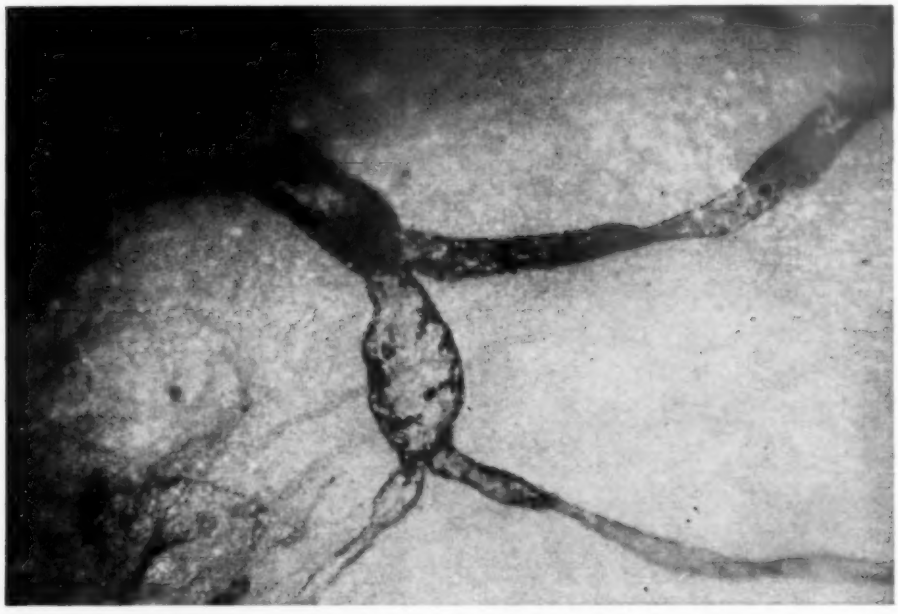

Fig. 2.—Dye-filled lymph vessels (×225; reduced ⅓).

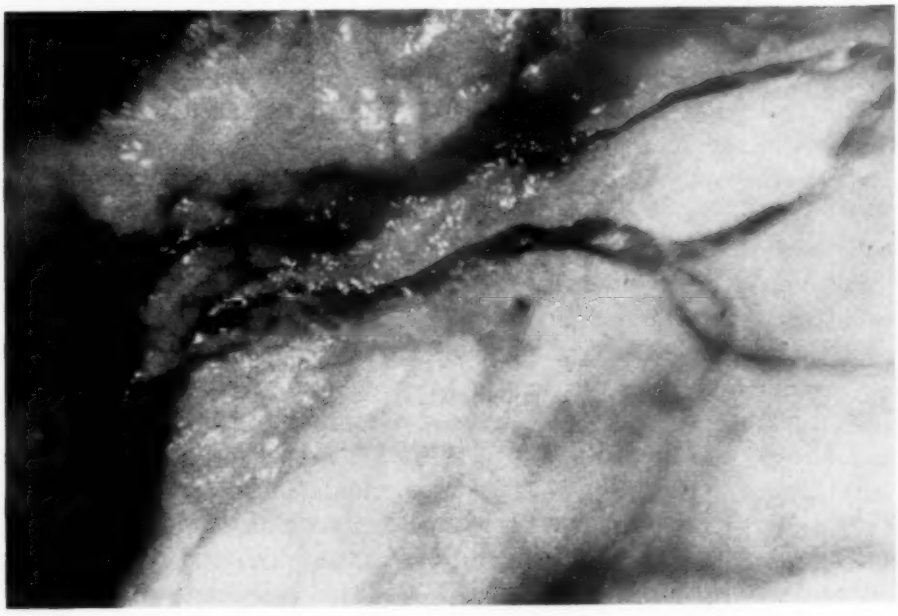

Fig. 3.—Dye-filled lymph vessel and node (×225; reduced ⅓).

RESULTS

The first-echelon nodes which were observed to fill from injections into the pancreas are shown in Table I. These are listed in order of number of specimens in which one or more nodes of the particular group were observed to fill. The group in which there was most frequent nodal filling is first, the group with the least filling last.

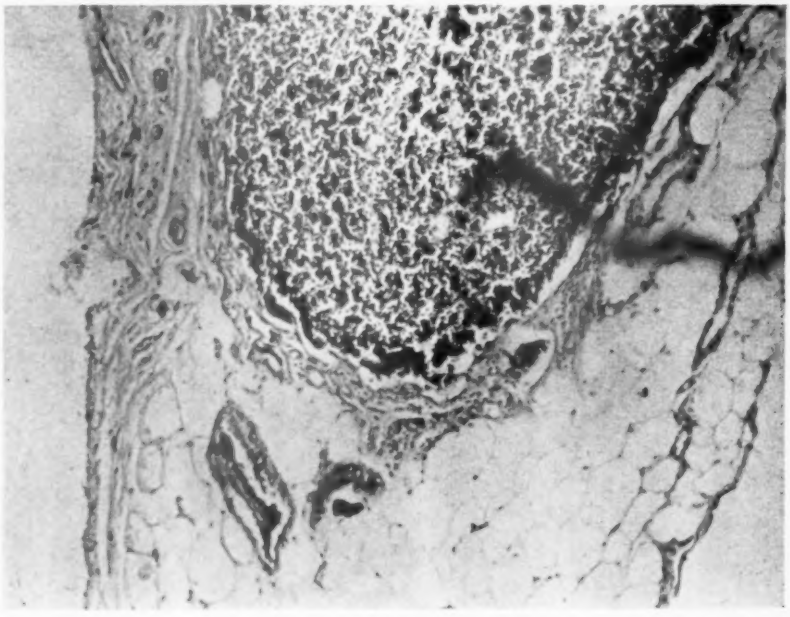

Fig. 4.—Dye in lymph vessels and lymph node (×400; reduced ⅓).

No doubt this method of classification presents an erroneous impression of the frequency of involvement in so far as practical application is concerned. As can be seen in Figs. 5 and 6, injections into the head of the pancreas, inferior to the attachment of the mesocolon to the head, with few exceptions, filled vessels which travel directly to the nodes about the superior mesenteric vessels and the origin of the middle colic artery, whereas injections into the head superior to the mesocolon attachment traveled in greater number to the infrapyloric, pancreaticoduodenal, and suprapancreatic nodes. There is, of course, considerable overlapping. Vessels from all portions of the head, but especially from the area of junction between head and neck, may terminate in the juxta-aortic nodes. The suprapancreatic and infrapancreatic nodes receive vessels from the adjacent portions of the entire length of the neck and body, as well as part of the tail. Since this constitutes the bulk of the gland, and since the total number of injections was greater in these areas than in the head (Fig. 6), it becomes apparent that actually the superior mesenteric and mesocolic nodes are just as frequently, if not more frequently, involved.

Injections into the posterior surface of the head and neck were observed to fill vessels running to the juxta-aortic nodes and the pancreaticoduodenal

nodes, into the posterior surface of the body, the suprapancreatic or infrapancreatic nodes, and into the tail, the nodes of the splenic hilus and gastropancreatic fold.

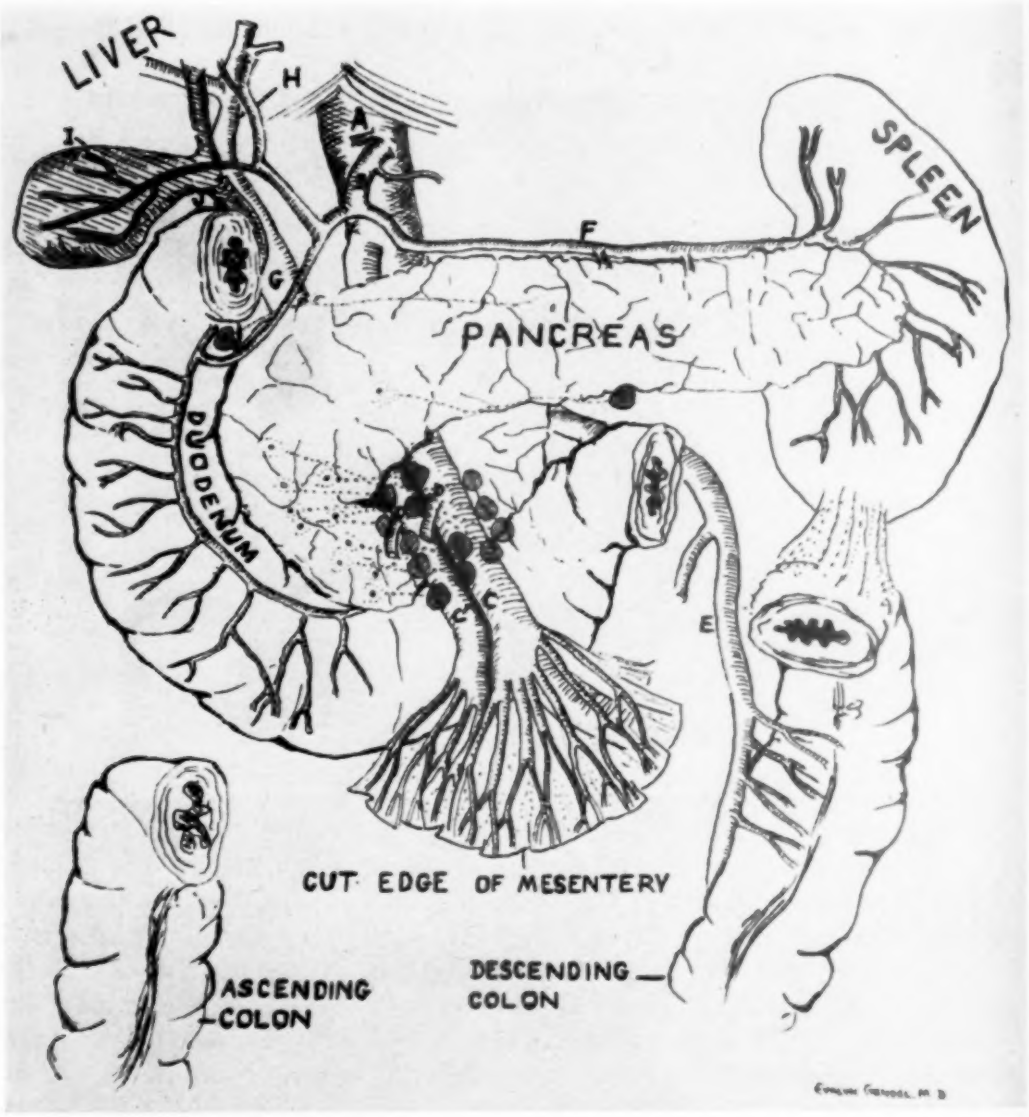

Fig. 5.—Composite diagram showing root of mesentery nodes and preaortic (= celiac) nodes. *A*, Aorta; *B*, celiac axis; *C*, superior mesenteric artery; *C'*, superior mesenteric vein; *D*, mid-colic artery; *D'* mid-colic vein; *E*, inferior mesenteric vein; *F*, splenic artery; *G-H*, portal vein; *I*, gall bladder; *J*, cystic duct.

Previous investigators have made distinctions between anterior and posterior pancreaticoduodenal nodes. It appears that these nodes about the superior and inferior pancreaticoduodenal arteries are not practically divisible into anterior and posterior groups. In the same connection, it is believed that the retropyloric node, which was found to lie adjacent to the pylorus, between it and the head of the pancreas with the contained common bile duct, can be

considered as the uppermost unit of the pancreaticoduodenal chain. The so-called infrapyloric node is no doubt separate from this group, and probably most often is found in relation to the anterior branch of the supraduodenal

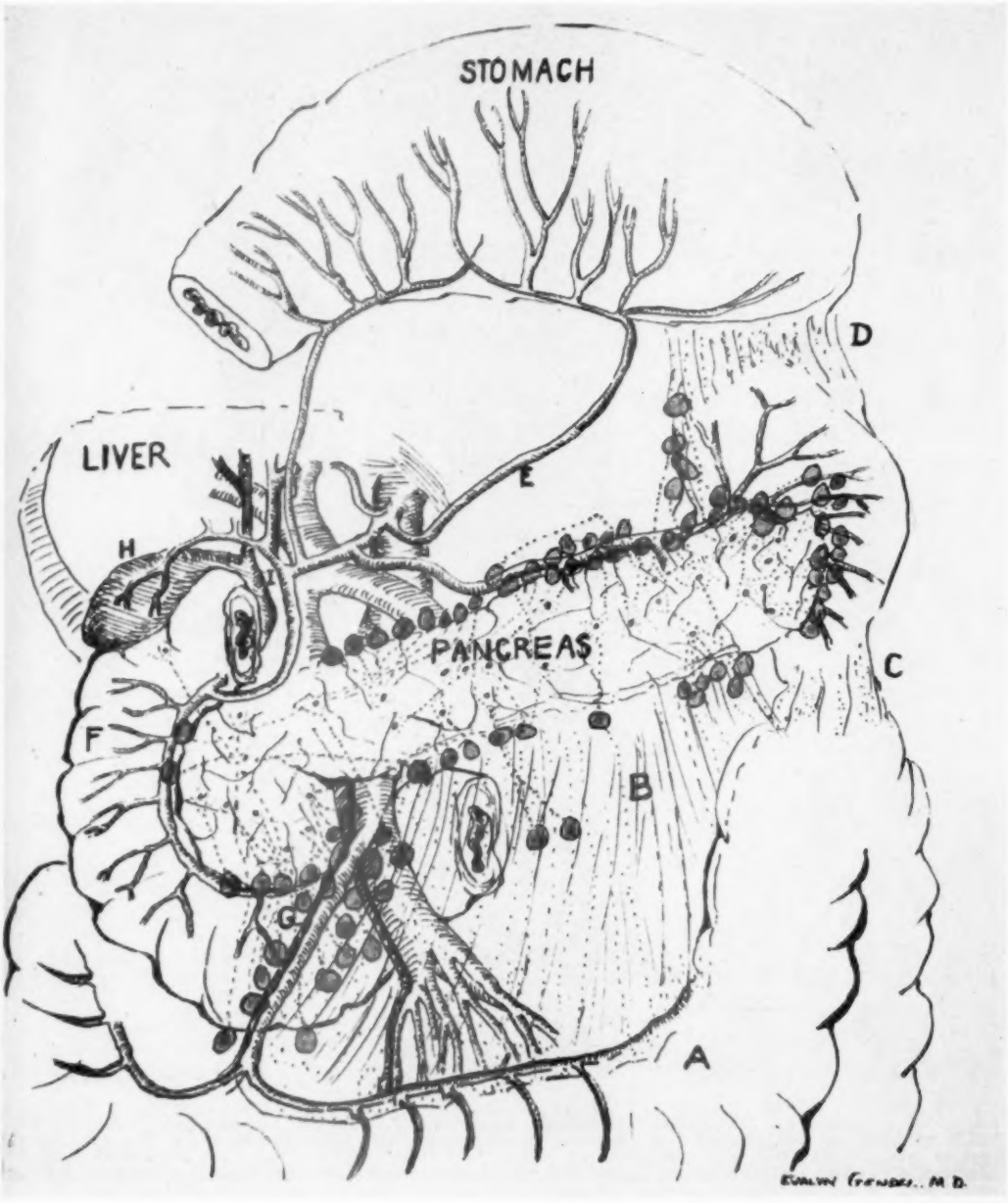

Fig. 6.—Composite diagram showing transverse mesocolon nodes. *A*, Transverse colon; *B*, transverse mesocolon; *C*, phrenocolic ligament; *D*, gastrosplenic ligament; *E*, left gastric artery; *F*, duodenum; *G*, mid-colic artery; *H*, gall bladder; *I*, common bile duct.

artery of Wilkie. The suprapancreatic nodes are in relation to the splenic vessels and the infrapancreatic nodes are, of course, actually within the leaves of the mesocolon.

Filling of the node of the epiploic foramen, such as Rouviere[23] described, was not observed, nor was filling of any retroaortic nodes observed. These studies also failed to demonstrate any direct anastomosis between the lymphatics of the duodenum and pancreas, as reported by Bartels.[1, 2] Moreover,

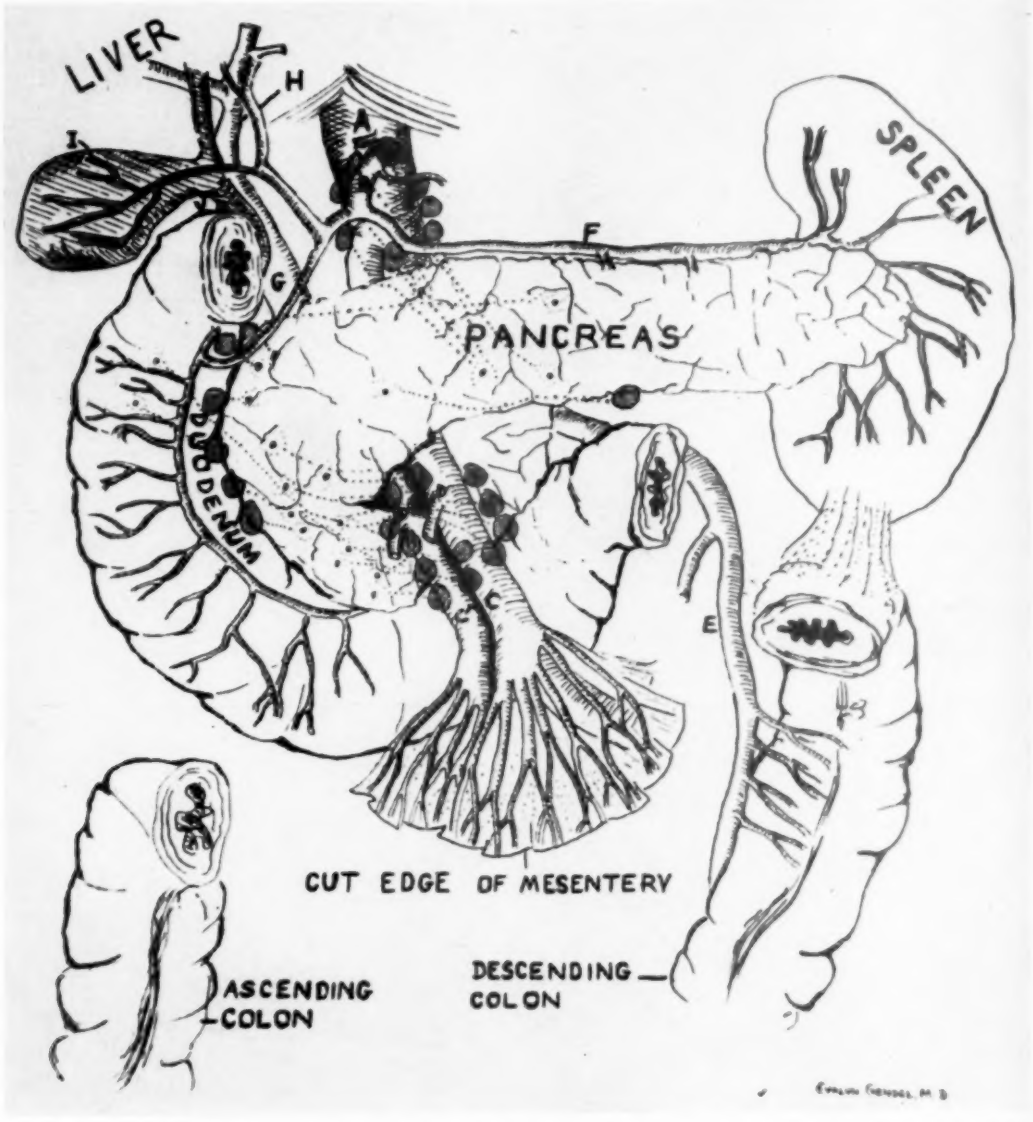

Fig. 7.—Diagram demonstrating filling of superior mesenteric nodes from injections into head inferior to attachment of mesocolon. Also shows infrapyloric node and infrapancreatic node filled from distant injection. *A*, Aorta; *B*, celiac axis; *C*, superior mesenteric artery; *C'*, superior mesenteric vein; *D*, mid-colic artery; *D'*, mid-colic vein; *E*, inferior mesenteric vein; *F*, splenic artery; *G-H*, portal vein; *I*, gall bladder; *J*, cystic duct.

connections between channels which were observed to run from the duodenum across the pancreas to terminate in juxta-aortic, mesocolic, or mesenteric nodes, and lymphatic vessels of the pancreas could not be demonstrated.

Although some investigators have doubted the existence of nodes in the gastropancreatic fold of the gastrosplenic ligament, on four occasions these

nodes were filled from injections near the superior border of the tail of the pancreas (Fig. 6).

TABLE I. FIRST-ECHELON NODES OBSERVED TO FILL FROM INJECTIONS INTO THIRTY PANCREATIC SPECIMENS

GROUP	NO. OF SPECIMENS	NODE	NO. OF FILLED NODES
1	17	Suprapancreatic	40
2	8	Infrapancreatic	21
	8	Superior mesenteric	16
	8	Mesocolic	24
3	7	Splenic hilar	23
4	5	Pancreaticoduodenal	14
	5	Interaorticocaval	22
	5	Preaortic	16
5	4	Left lateral aortic	14
	4	Left gastropancreatic	4
	4	Retropyloric	4
6	3	Infrapyloric	3

Of importance is the observation of lymphatic vessels arising from an injection into the head of the pancreas and traveling a considerable distance to the left to empty into an infrapancreatic node at the inferior border of the body of the gland. Vessels were also observed arising from the neck and body which traveled across the head to empty into the infrapyloric gland (Fig. 7). On the basis of these observations, a classification of the regional (first-echelon) lymph nodes of the pancreas is proposed (Table II).

TABLE II. PROPOSED CLASSIFICATION OF REGIONAL LYMPH NODES OF THE PANCREAS

1. Suprapancreatic
2. Infrapancreatic
3. Superior mesenteric
4. Mesocolic
5. Splenic hilar
6. Pancreaticoduodenal
7. Infrapyloric
8. Gastropancreatic
9. Juxta-aortic
   a. Left lateral aortic
   b. Interaorticocaval
   c. Preaortic (includes nodes about celiac axis)

DISCUSSION

Although removed from the "hermitage" it inhabited a decade ago, the diseased pancreas yet remains obstinate to surgical attempts to restore it to normal, especially if the disease be cancer. In spite of tremendous advances in recent years in preoperative and postoperative treatment, the advent of vitamin K and its use in the icteric patient, increased knowledge of pancreatic physiology, and more adequate means with which to combat surgical shock and infection, malignant neoplasms of the pancreas still constitute one of the most hopeless conditions confronting the surgeon today.

Since the first attempt at radical removal of the head of the pancreas and duodenum for carcinoma of the head of the pancreas by Codivilla[15] in 1898,

sporadic reports of surgical attacks on this organ have appeared. Although Kausch[23] reported the first successful pancreatoduodenectomy for carcinoma of the ampulla of Vater in 1912, it remained for Whipple[42] in 1935 to revive interest in the procedure which now bears his name. Numerous surgeons have since reported "operative" success with this procedure, but long-term results in patients with carcinoma originating in the head of the pancreas have been most discouraging. This is evidenced by the fact that, at this writing, reports of only eight cases of patients with carcinoma of the head of the pancreas who have survived as long as five years postoperatively are to be found in the literature,[4, 8, 14, 25, 28, 39, 41] and at least two of these were dead at the end of five years and four months. Earlier diagnosis and complete removal of involved tissue still appear to be the prime objectives in altering favorably this bleak outlook in carcinoma of the head of the pancreas.

Cattell,[6, 7] among others,[10, 40] recently suggested total pancreatectomy as one means of removing more involved tissue. As yet, this procedure has been applied largely to far-advanced lesions, and when it has been used in more favorable cases, sufficient time has not elapsed to evaluate the results. The present anatomic study of the pancreatic lymphatics has revealed instances in which lymphatic channels led directly from the head of the pancreas to nodes located at the inferior border of the body. This would indicate that often removal of only the head of the pancreas for carcinoma located in that portion might not be sufficient. In addition, it is thought that the clinical interpretation of lymph node involvement is in error in at least 30 per cent of cases. This has led to almost routine lymph node dissection in carcinoma of the lung, breast, stomach, colon, and rectum. These operations attempt to include the intervening lymph vessels as well as the regional nodes, even when these nodes are not clinically involved. The end results in pancreatoduodenectomy for carcinoma of the head of the pancreas would seem to indicate the need for more complete removal of the regional nodes and lymph pathways. Many authorities[5, 7, 29, 30] have been of the opinion that the presence of enlarged regional nodes provides a distinct contraindication to the performance of pancreatoduodenectomy. Others[9] have not shared this point of view, but cases with involvement of the superior mesenteric vein via adjacent involved lymph nodes have been universally considered unresectable. Indeed, most surgeons plan their procedure in such a way as to be able to examine thoroughly this important structure before reaching the "point of no return" and a more simple short-circuiting procedure can still be accomplished. Child[9] has called this the weakest as well as the most frustrating point in the entire operative attack on pancreatic cancer, and expressed hope that in the future some successful method of avoiding the necessity of preserving this vessel might be devised.

In 1947 Brunschwig[3] reported a case in which the portal vein and the superior mesenteric vein were ligated in removal of extensive carcinoma of the pancreas; death occurred on the tenth day, presumably of peritonitis, and at post-mortem examination the intestines appeared to have been normal and

viable. Several years previously, Schnug[38] reported a case of gunshot wound which so damaged the superior mesenteric vein that repair was not possible and ligation was performed; immediate heparinization was accomplished and at reoperation later a fairly normal-appearing intestine was observed.

The results of experimental occlusion of the superior mesenteric vessels in dogs were reported in 1950 by Nelson and Kremen.[27] They noted that death from peritonitis occurred from eleven to twenty hours after occlusion of the superior mesenteric artery, and occlusion of the superior mesenteric vein resulted in death due to shock in four hours. The use of Sulfasuxidine or streptomycin to reduce the bacterial flora in the intestinal tract prior to occlusion of the vessel, as well as preoperative heparinization, extended the time of safe occlusion. Six of eight dogs given heparin prior to ligation of the superior mesenteric vein survived. Later sacrifice of several of these animals revealed a normal intestine despite the fact that the vein was still occluded. That important differences exist between the intestinal blood supply in man and in the dog is not denied. However, these differences are significant only when relatively short segments of intestine are deprived of their blood supply and not in cases of massive ligation of the blood supply to the entire small intestine. Collateral channels exist between the inferior mesenteric veins through the hemorrhoidal plexus to the systemic venous system, through omentum and abdominal wall collaterals, through retroperitoneal, lumbar, and azygos veins, and between pancreaticoduodenal and superior mesenteric vessels.

Moore, Sako, and Thomas[26] in 1951 published the first report of resection and reanastomosis of the superior mesenteric vein in a patient undergoing pancreatoduodenectomy; both vein and artery were clamped for a period of ninety-five minutes. If reanastomosis is not possible in such cases, anastomosis to the vena cava or inferior mesenteric vein, or a vein graft might be applicable. Such considerations must keep in view the fact that, contrary to most textbook descriptions, in many instances, the inferior mesenteric vein empties into the superior mesenteric vein.

More recently, Child and co-workers[11] published a report of experimental observations following sudden and complete occlusion of the portal vein in fifty-two *Macaca mulatta* monkeys. The mortality in this experimental series was 14.6 per cent. It was shown that immediately following occlusion of the portal vein, the portal pressure rose rapidly and that dissection at this time about the pancreas and duodenum resulted in uncontrollable hemorrhage. Later studies, however, revealed that within twenty-four hours after occlusion, the portal pressure began to fall and within eight to ten days had stabilized at essentially the preocclusion level. Additional experiments were then performed in which a two-stage operation was accomplished. The portal vein was first occluded and eight to ten days later the pancreas, duodenum, portal vein, and superior mesenteric vein were resected. Because of the lowered portal pressure, there was much less bleeding during the second stage procedure in the majority of cases. These authors later performed this operation on two patients, both of whom had uneventful postoperative courses for thirty-nine and twenty-one days (at the time of the report).

Successful resection of the portal vein and anastomosis of the superior mesenteric vein to the vena cava during a one-stage pancreatoduodenectomy for carcinoma of the head of the pancreas has been reported by McDermott.[24] According to Daniel,[16] Sweet has performed this same procedure on two occasions. McDermott's patient was living four months after operation, and apparently no serious sequelae attributable to the Eck fistula had developed at that time. The long-term follow-up observation of these cases will be of great interest, since heretofore there has been no accurate knowledge of how the human system reacts to such artificial extrahepatic portal block. Portacaval shunts performed for relief of portal hypertension are not comparable, since these patients have a pre-existing portal block with consequent extensive development of collateral circulation in the accessory portal system.

Daniel[16] presented a preliminary experimental report on bridging defects in the portal and superior mesenteric veins by use of plastic tubes and vascular grafts. With perfection of technique and development of additional aids to reduce the occlusion time while placing the graft, this method seems to hold the greatest promise for re-establishing the portal blood flow.

Malignant growths spread by direct extension, by blood vessel embolism, and by way of the lymphatics. The manner of metastasis varies with the type of tumor and its location. In carcinoma, metastasis occurs predominantly through the lymphatics. The end results of surgical treatment of carcinoma depend on the ability to remove all malignant cells. If the tumor can be removed locally, and if blood vessel embolism has not occurred, cure will then be determined by the extent of lymphatic spread. Gilchrist[18] has stated that post-mortem studies of patients dying within two weeks of resection for carcinoma of the colon or rectum repeatedly showed that resection had "just missed" removing all tumor-bearing nodes. A resection only 1 or 2 cm. wider would usually have removed all tumor-bearing nodes. There was no evidence of distant metastasis in these specimens. McDermott mentioned that autopsies on patients who died some time following pancreatoduodenectomy for cancer of the pancreas demonstrated massive local recurrence but no distant metastases.

The extreme importance of making the widest possible resection of the lymphatics which drain a carcinomatous focus has long been evident, and in dealing with cancer of pancreatic origin, a thorough and accurate knowledge of the anatomy of the lymphatic pathways of the pancreas is essential if the plan of more radical removal of pancreatic tissue and regional nodes is to be applied in a manner similar to the present-day radical mastectomy or Wertheim hysterectomy.

The results of this study make evident the fact that even more radical surgical procedures than those presently employed for carcinoma of the head of the pancreas must be undertaken if a survival rate high enough to justify surgical intervention is to be achieved. Observations at necropsy in those dying from metastasis subsequent to pancreatoduodenectomy lend support to this view. The almost certain involvement of the nodes about the superior

mesenteric vein by lesions in the pancreatic head makes their removal mandatory if cure is to be obtained. The present study has shown that the first-echelon pancreatic nodes in relation to the mesenteric vessels are those about the origin of the artery and termination of the vein as they lie posterior to the pancreas and cross the third portion of the duodenum. It seems, therefore, that radical operation for carcinoma of the head of the pancreas should include resection of this short and early involved segment of superior mesenteric vein.

Because of the close proximity of the mid-colic vessels to the terminal portion of the superior mesenteric vein and the likelihood of involvement of the mid-colic lymph nodes, we believe that the operative plan should also include the possible necessity of sacrificing these vessels. According to Rankin and Graham,[31] in more than 100 specimens examined, there was no failure of anastomosis of the left colic and middle colic arteries via the marginal artery. In fact, in all but 5 per cent of forty specimens, the marginal artery was continuous from ascending colon to sigmoid colon, and in these, the failure of anastomosis was between the ileocolic and right colic arteries. It can be suspected, therefore, that the viability of the transverse colon might not be impaired by ligation of these vessels close to their junction with the superior mesenteric vessels. If, on the other hand, by the time the procedure is nearing completion it becomes obvious that the blood supply to a portion of the transverse colon is jeopardized, resection and anastomoses can then be accomplished. Since lymphatic vessels have been seen coursing from the head of the pancreas to infrapancreatic nodes inferior to the right portion of the body of the gland, such an operation would also include removal of the neck and as much of the right half of the body as possible without interference with the splenic vessels. In some instances, total pancreatectomy and splenectomy would be indicated.

With full realization that additional hazards would be added to an already formidable operation, but with the firm belief that only by extending the scope of the operative attack upon carcinoma of the head of the pancreas can any real hope for cure be entertained, the following operative plan is proposed: (1) exploration, transduodenal biopsy; (2) elevation of duodenum and head of pancreas; (3) division of right half of gastrocolic omentum; (4) freeing of hepatic flexure and transverse colon; (5) exposure of superior mesenteric and mid-colic vessels; (6) division of gastrohepatic omentum; (7) division of right gastric and gastroduodenal artery; (8) exposure of portal vein and superior border of body of pancreas; (9) division of stomach in prepyloric area; (10) division of common duct; (11) division of jejunum and freeing of proximal jejunal mesentery; (12) delivery of proximal jejunum and fourth portion of duodenum to the right of the superior mesenteric vessels; (13) resection of superior mesenteric vein; (14) resection of mid-colic vessels if involved; (15) division of the pancreas at the junction of the body and tail (in some instances total removal may be preferable); (16) removal of specimen; (17) reanastomosis or grafting of superior mesenteric

vein defect; (18) end-to-end choledochojejunostomy; (19) end-to-side pancreatojejunostomy; (20) gastrojejunostomy; (21) resection of transverse colon and end-to-end anastomosis if viability is impaired; and (22) insertion of drain and closure of wound.

SUMMARY

A detailed study of the gross anatomy of the lymphatics of the pancreas was made in thirty human cadavers. The results of the study indicate that a more extensive operative procedure than that presently employed is indicated in the treatment of carcinoma of the head of the pancreas if the survival rate is to be improved.

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END-TO-END ASEPTIC INTESTINAL ANASTOMOSIS IN INFANTS AND CHILDREN

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WHEN a surgeon encounters an intestinal lesion which requires resection, he may either exteriorize the intestine as an ileostomy or as a colostomy, or restore intestinal continuity with an anastomosis. While infants and children tolerate ileostomy and colostomy satisfactorily, these procedures commit the patient to a second operation which prolongs the total hospitalization and may be an increased hazard to the patient. With the advent of antibiotics and improved operative techniques, the trend in caring for adult patients has been to perform resection and primary anastomosis rather than exteriorization operations. I should like to report our experience with a series of thirty-two infants and children who were treated with intestinal resection and end-to-end anastomosis. This technique was preferred to side-to-side anastomosis because it consumed less time and obviated the occasional late complication of dilatation and ulceration of the blind end of bowel beyond a side-to-side anastomosis. These blind pockets may dilate to an enormous size and cause abdominal pain. End-to-end anastomosis also permits an aseptic technique which has some advantages over an open anastomosis. From a physiologic standpoint, end-to-end anastomosis replaces the intestinal segments in a normal anatomic relationship, which probably accounts for the prompt return of intestinal function which we have observed in our patients. Side-to-side anastomosis achieves a larger stoma, but the size of the intestine adjacent to the side-to-side stoma determines its functional size, and in this important respect it is not appreciably larger than an end-to-end anastomosis.

The pathology of the thirty-two infants and children on whom end-to-end intestinal anastomosis was performed was as follows: seven closures of ileostomy or colostomy; five irreducible intussusceptions; four atresias of the small intestine; three congenital bands with intestinal obstruction and perforation; two strictures of the small intestine; two Meckel's diverticula with adjacent pathology of the intestine requiring resection; and one diverticulum of the colon.

The preoperative management of all these patients was fundamentally the same. They were given fluids and, in some instances, blood. Intestinal intubation was started either with a child's size Miller-Abbott tube or with a smaller plastic tube; however, operation was not delayed by a prolonged attempt to secure the tube's passage into the small intestine.[1] Most of the patients were given open-drop ether anesthesia, although premature infants and a few extremely sick patients received local anesthesia. The operation was performed

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through a right rectus muscle-retracting incision, except in the five patients with irreducible intussusceptions. A large, high McBurney's incision was used on these patients. If we encountered intussusception or a loop of intestine caught with a band with an area of questionable intestinal viability, resection was performed to prevent a possible postoperative perforation. Obviously, a large majority of patients with intussusception and intestinal obstruction due to congenital or postoperative bands can be treated without resection.

The anastomosis technique which we used was essentially that described some years ago by Collins,[2] Horine,[3] and more recently by Dennis,[4, 5] except that the bowel proximal to the obstruction was decompressed, particularly where the intestinal dilatation was excessive. To decompress the bowel we used a trocar or an aseptic aspirator which we described a number of years ago.[6] It consists of a double-walled tube which can be attached to the intestine by placing suction on the space between the walls (Fig. 1). An opening can be made into the distended intestine by inserting a scalpel through the tube itself. The intestine can be decompressed by suctioning intestinal contents through the incision, into the tube, and out through a side arm attached to a source of suction. The aseptic aspirator has two advantages over the trocar in that there is no contamination, and it can be manipulated to prevent clogging. The opening in the bowel used for this drainage was resected, together with the necrotic segment of intestine. Decompressing the bowel proximal to the obstruction reduced the size of the intestine, which in turn facilitated closure of the abdomen, and probably promoted early intestinal function. If the bowel is decompressed with care, especially if the aseptic aspirator is used, the danger of contamination and postoperative infection is nil. When the bowel had been decompressed, clamps were placed across it distal to the lesion and proximal to the area of decompression. Ordinary small hemostats with even serrations the full length of the jaw were used. Enterostomy clamps were not applied because the intestine might have been damaged and the return of subsequent intestinal function delayed. On the dilated side, clamps were placed at right angles with the long axis of the intestine. Distal to the point of obstruction, the clamp was placed at an angle sufficient to make this cut surface approximately equal in size to the cut end of intestine proximal to the lesion.

Before making the anastomosis in the four infants with intestinal atresia, six to eight inches of the enormously dilated intestine proximal to the atresia was resected. The dilated and hypertrophied intestine probably would never return to normal size and function, and probably its resection contributed to the patients' smooth postoperative course. Another important reason for resecting the dilated segment was to secure bowel whose size more nearly approximated the intestine beyond the atresia.

The intestine beyond the atresia was dilated by injecting normal saline solution through a fine needle inserted into the lumen. To compensate further for the smaller size of the intestine distal to the atresia, clamps were placed across the intestine at an angle so that the cut end of the intestine would approximate the size of the bowel at the point of resection proximal to the atresia.

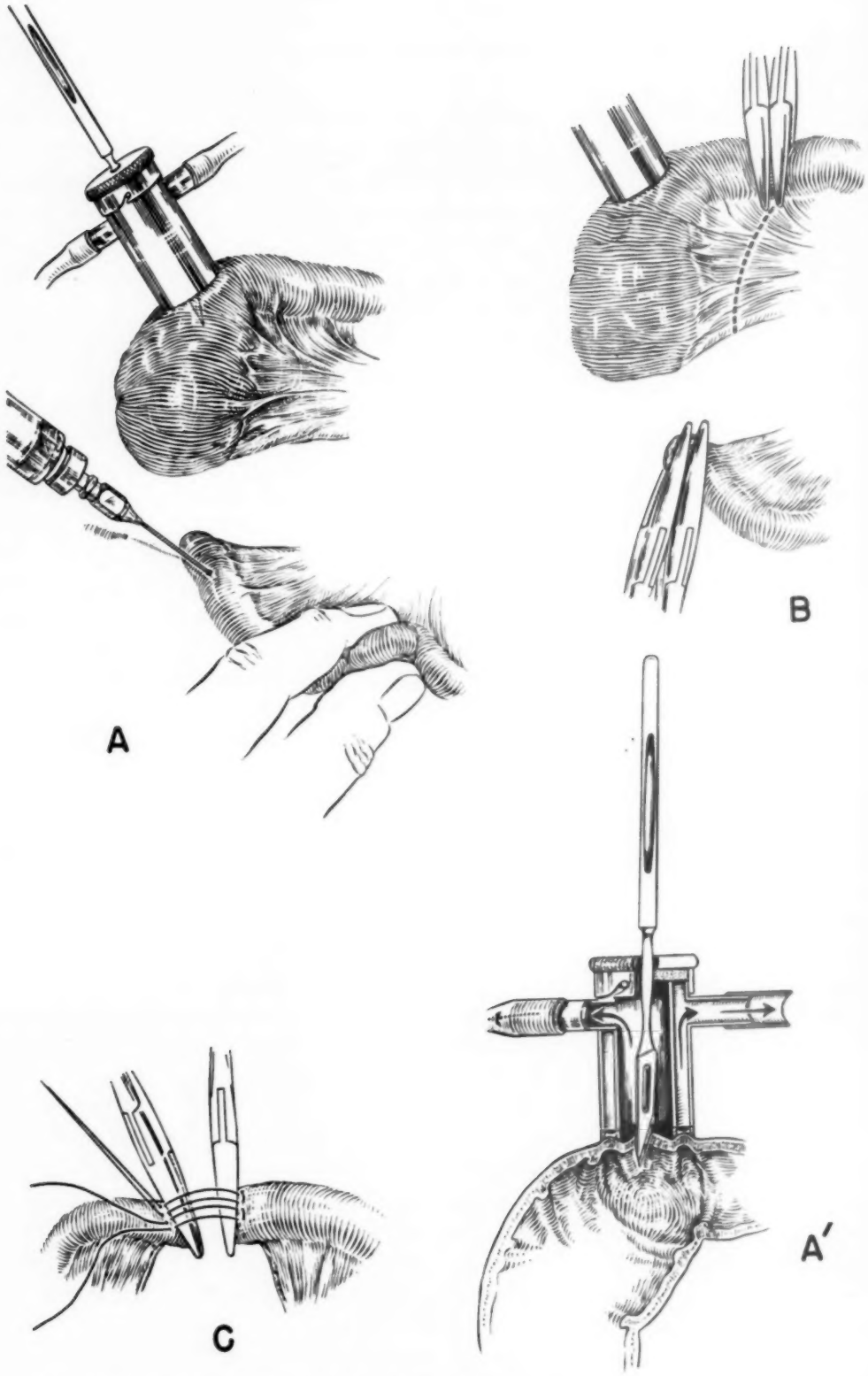

Fig. 1.—*A*, The intestine proximal to the obstruction is decompressed with the aseptic aspirator. Saline solution is injected into the intestine below the atresia to enlarge its size. *A′*, A diagrammatic drawing of an aseptic aspirator. Suction between the two tubes attaches the instrument to the intestine. The scalpel inserted through a rubber diaphragm perforates the intestinal wall and decompression occurs through the inner tube of the instrument. *B*, After decompression of the dilated intestine, 6 to 8 inches of the bowel is resected. This permits the clamps to be placed across the intestine where it is only slightly larger than normal. Clamps are placed at an angle, so that the cut surface will more nearly equal in size the proximal intestine. *C*, Interrupted mattress sutures are placed on one side.

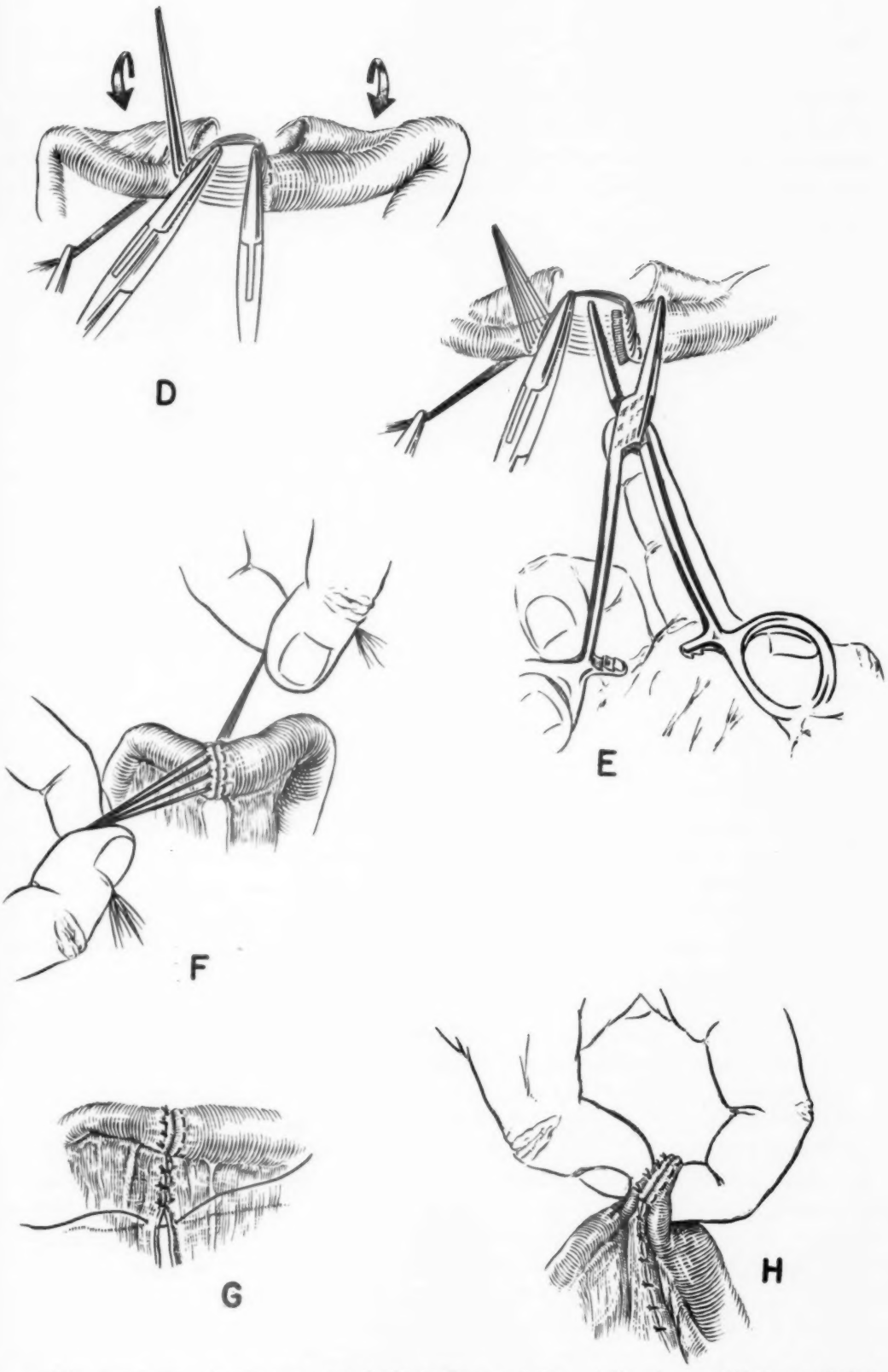

Fig. 2.—*D*, The clamps are rotated 180 degrees and the suturing is completed, care being taken that the sutures are passed around the ends of the clamps. Unless this precaution is taken, it is difficult to remove the clamps without opening the lumen. *E*, Removal of the clamps is unimpeded by the sutures. *F*, The sutures are carefully pulled together and tied. *G*, The mesenteric defect is closed with interrupted black silk sutures. *H*, The diaphragm is opened by placing the anastomotic ring between the thumb and index finger.

We did not use a cautery in cutting the intestine, but divided the bowel with a phenol knife, removing the excess phenol from the cut end of the intestine with an applicator moistened with 90 per cent alcohol. Even though we dispensed with cautery, bleeding from the anastomosis was insignificant, and in no patient was there a significant fall in the red blood count or tarry stools postoperatively.

Fig. 3.

Fig. 4.

Fig. 3.—Photograph of ileal atresia showing the segment which we resect prior to anastomosis. A clamp has been placed on the intestine below the atresia.

Fig. 4.—Photograph of completed anastomosis.

On the mesenteric side of the bowel, all of the fat and vessels were carefully removed to leave a smooth intestinal surface of 2 mm. for sutures. The suturing was performed with atraumatic needles attached to lightly waxed 00000 black silk. As a final compensation for discrepancy in the size of the two segments, Halsted mattress sutures were placed close together on the smaller segment of intestine and at wider intervals on the larger end (Fig. 2). On the first side they were placed straight across; then the clamps were rotated 180 degrees to expose the other side of the intestine. Here sutures were placed around the ends of the clamps so that the intestinal clamps were free and could be removed without impinging on the sutures and inadvertently opening the crushed ends of the intestine. Despite this precaution, in 10 per cent of our anastomoses the seal broke when the clamps were removed, and slight contamination occurred from the opened ends of the intestine. This did not result in complications, but the procedure is neater and cleaner if the ends of intestine remain sealed until the anastomosis is completed. When the clamps had been removed, gentle traction was placed on the sutures and the two segments were approximated. The sutures were then tied and cut. Usually, an extra suture was needed on the mesenteric and antemesenteric sides of the anastomosis to complete the suture line. All the sutures had to be carefully placed to avoid perforating the mucosa. However, they were no more difficult to place than the second row of sutures of a conventional open anastomosis. The mesenteric opening was closed with interrupted silk sutures, and all rough edges turned in to prevent postoperative adhesions. The diaphragm formed by the sealed ends of intestine was

broken by placing the index finger on one side of the suture line and the thumb on the other, and invaginating the intestinal wall through the stoma. Patency of the anastomosis was demonstrated by gently pushing intestinal contents through it. Closing the abdomen presented no difficulty because the dilated bowel had been decompressed (Figs. 3 and 4).

Of the thirty-two patients who were submitted to operation, twelve were 1 month old or less; eight were from 2 to 6 months old; one was 8 months old; and eleven were 1 year or more. Thus, over one-half of them were under 6 months old, and almost 40 per cent were less than 1 month of age. Their immediate postoperative course was most gratifying: seven were discharged from the hospital within one week of operation; fourteen within two weeks after operation; four within three weeks; and the remaining four, one of whom was premature and underweight, after twenty-one days. As soon as peristalsis was audible, and this was usually twenty-four hours after operation, feedings of 5 per cent glucose in water were started. If this was tolerated for twenty-four hours, a diluted formula was offered. On the third day of oral feedings, the patients received a full formula.

Three postoperative deaths occurred. In one patient with mesenteric occlusion, only a 3 cm. segment of proximal jejunum was viable; the rest of the small intestine except 2 cm. of terminal ileum was necrotic, and there was extensive fecal contamination from a perforation. Resection with end-to-end anastomosis was performed, but the patient died twenty-four hours after operation. The anastomosis was demonstrated to be intact at the post-mortem examination. Death was attributed to overwhelming peritonitis. In another patient with a congenital heart, death occurred twelve hours after operation, and again a post-mortem examination revealed the anastomosis to be sound. The third death occurred in a newborn infant with extensive generalized peritonitis resulting from a perforation of the proximal ileum. A resection with ileostomy was performed. The high ileostomy permitted a troublesome loss of intestinal fluid, and the baby lost weight. The ileostomy was closed with an end-to-end anastomosis. Death was due to chronic peritonitis with multiple small intra-abdominal abscesses. In retrospect, this patient might have fared better with an initial end-to-end anastomosis.

In all the other patients, end-to-end anastomosis proved adequate. Technically, it is a straightforward operation which does not require a long period of time in the operating room. It has proved successful, with a satisfactory mortality rate, and no significant postoperative complications in this series of thirty-two infants and children.

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FAT EMBOLISM*

The Detection of Fat Emboli in the Circulating Blood

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INTRODUCTION

FAT embolism, to paraphrase Winston Churchill, is a riddle wrapped in a mystery inside an enigma. It has remained so, since Zenker first described its appearance at the autopsy table almost 100 years ago. Fat embolism has resisted the efforts of surgeons to define it as a clinical entity, and there are some who, even now, deny that such a diagnosis can be made on clinical grounds alone. The experimental study of this phenomenon was begun before its pathology was known. Laboratory investigation has been more productive of frustration than of understanding, and the exact nature of fat embolism has, so far, eluded our comprehension. One of the chief obstacles in the study of fat embolism has been the lack of methods for demonstrating the emboli themselves as they circulate in the blood stream. Such a method is now available and should provide a new tool with which to pry into this perplexing question.

The fat droplets of physiologic lipemia have been studied by dark-field illumination under the microscope for nearly 200 years.[2] These chylomicrons do not exceed 1 micron in diameter and therefore give rise to no embolic phenomena. Scuderi[11] was able to demonstrate fat droplets about 14 microns in diameter in the blood of dogs shortly after the intravenous injection of olive oil. He was unable to find any similar fat droplets in blood samples obtained from twenty-five patients with fresh fractures. He felt, however, that such fat droplets would be found in patients suffering from fat embolism, and that such a finding would be of diagnostic importance.

In 1948, Monson[6] studied 109 patients with fractures of the long bones. A diagnosis of fat embolism was made clinically in nine. Blood samples were drawn at various intervals from the peripheral veins of these patients. After centrifugation, a drop of supernatant plasma was examined for large fat droplets. In six of the nine cases, fat globules, 12 to 20 microns in diameter, were found; in five of the six cases, on more than one occasion. Monson concluded that the finding of fat globules of 12 microns or greater diameter was of real significance in the diagnosis of fat embolism. This opinion was supported by the finding of fat in the urine of five of these six patients, and by the demonstration of typical fat embolism at the autopsy of the one patient in this group who died of his injuries.

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THE METHOD

This method is dependent upon the use of a water-soluble fluorescent fat stain, phosphin 3R. The use of fluorochromes is not new, and the technique of fluorescence microscopy has been well described.[3-5, 9] The distribution of vitamin A in tissues,[8] as well as the identification of oils causing lipoid or aspiration pneumonia,[12, 13] has been studied by fluorescence microscopy. Tubercle bacilli can be identified in sputum and gastric washings by the use of a fluorochrome.[10] Phosphin 3R belongs to the xanthine group of stains,[1] and is especially suited for staining fat emboli, since it is water soluble, in contrast to the sudan stains and scarlet red, which are prepared in alcohol or acetone solutions.

A sample of blood (3 to 5 c.c.) is drawn from a peripheral vein into an evacuated tube containing an anticoagulant. To this sample is added 0.5 c.c. of a 1 to 1,000 water solution of phosphin 3R. The sample is then centrifuged for twenty minutes at 2,500 r.p.m. After the tube is removed from the centrifuge, the tip of an applicator stick is touched to the meniscus of the supernatant plasma, and the small drop which clings to the stick is then deposited upon a clean glass slide in a series of three or four "puddles." Several drops can be removed from each sample in this manner. After the slides have dried, they are examined with the 16 mm. objective of a microscope equipped for fluorescence microscopy. The fat emboli can be recognized by their characteristic white fluorescence with a slight orange cast. They are well-defined globules ranging in diameter from 7 to 14 microns.

ANIMAL EXPERIMENTS

Fasting mongrel dogs of more than one year of age were used in these experiments. They were anesthetized with pentobarbital sodium (15 mg. per kilogram) given intravenously. Occasionally it was necessary to augment this basic anesthesia with another small increment. None of the animals was given ether. Fractures of both bones of the legs (radius and ulna, tibia and fibula) were produced by snapping the extremity over the edge of a vise. The fractures were transverse in character and were not badly comminuted. Blood samples to be examined for fat emboli were drawn from peripheral veins of uninjured extremities or from the internal jugular vein. At the end of each experiment the animal was killed by exsanguination. A blood sample was then obtained by aspirating the right atrium. After an autopsy, frozen sections were made from the lungs, brain, and kidneys. These were stained with phosphin 3R, using a method described elsewhere,[7] and examined for fat emboli. Only fat droplets appearing to be within the lumen of a vessel were considered to be fat emboli.

In a group of seven dogs, two blood samples were drawn as controls, one immediately after the anesthesia was begun; the second, thirty minutes later. One of the forelegs was then fractured, and after thirty minutes another sample was drawn. The remaining limbs were fractured at intervals of thirty minutes, a blood sample being obtained prior to each fracture. One-half hour

after the last fracture, the animals were sacrificed, and a last blood sample was obtained from the right atrium. An autopsy was then performed. The results of the experiment are presented in Table I.

TABLE I. THE INCIDENCE OF FAT EMBOLI IN THE BLOOD, LUNGS, BRAIN, AND KIDNEYS OF DOGS WITH FRACTURES OF THE LONG BONES

DOG	1ST CONTROL 0 MIN.	2ND CONTROL 30 MIN.	1ST FRACTURE 60 MIN.	2ND FRACTURE 80 MIN.	3RD FRACTURE 120 MIN.	4TH FRACTURE 150 MIN.	RIGHT HEART 180 MIN.	LUNG	BRAIN	KIDNEY
1	0	0	+	+	0	0	0	+	+	+
2	0	0	+	+	+	+	+	+	+	+
3	0	0	+	+	+	+	+	+	+	+
4	0	0	0	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	+
6	0	0	0	0	+	+	+	+	+	+
7	0	0	+	+	+	+	+	+	0	+

In a second group of eight dogs, the experiment was modified by the use of a tourniquet. In these animals, after an initial control sample was drawn, rubber tourniquets were applied to all four extremities, which were then fractured. The tourniquets remained in place for ninety minutes, and were then removed. In all these animals, fat emboli were found in blood samples removed from the jugular veins and from the right atrium, as well as in sections of the lungs, brain, and kidneys. There were no emboli in any of the samples obtained as controls prior to fracture.

In these two groups of animals, fifteen in all, fat emboli were seen in only one prior to fracture. After fractures of the long bones, fat emboli were found in the circulating blood of all of the animals. In every animal in which fat emboli were found in the blood, embolic fat was found in sections of the lungs and kidneys and, with one exception, the brain.

CLINICAL EXPERIENCE

A group of ten male volunteers was studied to determine whether or not the presence of an alimentary lipemia would interfere with the detection of fat particles larger than 6 microns in diameter. Lipemia was produced by the administration of 100 c.c. of a concentrated fat emulsion* orally to the fasting subjects. Blood samples were drawn prior to, and three hours after, the ingestion of the fat emulsion (Table II). None of the patients exhibited lipemia in the fasting state. Lipemia was produced in seven subjects three hours after the administration of the fat emulsion. In one of these patients, fat emboli could be detected at this time.

The major portion of the investigation was concerned with the study of seventy-eight patients on the orthopedic service undergoing elective surgery. These patients were selected for study rather than those with fresh fractures because (1) a more satisfactory control could be maintained in the uninjured patients and (2) the degree of trauma to the soft tissue and bone could be more accurately assessed. Blood samples were obtained from the peripheral veins

*Lipomul, furnished by The Upjohn Company.

of the fasting patients immediately after the induction of anesthesia. Similar samples were obtained at the end of the operation and during the immediate postoperative period. At least three specimens were obtained from each patient. The details of this study are presented in Tables III and IV.

TABLE II. THE EFFECT OF AN ALIMENTARY LIPEMIA UPON THE DETECTION OF FAT EMBOLI IN THE BLOOD

PATIENT	AGE (YR.)	ANTECIBUM		3 HOURS POSTCIBUM	
		PLASMA	EMBOLI	PLASMA	EMBOLI
1	16	Clear	0	Lipemia	0
2	17	Clear	0	Lipemia	0
3	14	Clear	0	Lipemia	0
4	12	Clear	0	Lipemia	0
5	20	Clear	0	Lipemia	0
6	17	Clear	0	Patient vomited	Emulsion
7	17	Clear	0	Clear	0
8	20	Clear	0	Lipemia	0
9	17	Clear	0	Lipemia	0
10	33	Clear	0	Clear	0

TABLE III. COMPOSITION OF STUDY GROUP

SEX:	Male: 37; Female: 41								
AGE:	Decade:	1	2	3	4	5	6	7	8
	No. of patients:	11	38	7	7	5	3	3	4
ANESTHESIA:	Pentothal-curare, ether, cyclopropane, spinal								
	58	11	7	2					

TABLE IV. THE DETECTION OF FAT EMBOLI IN THE CIRCULATING BLOOD ACCORDING TO OPERATION

OPERATION	+	0	OPERATION	+	0
Osteotomy, femur	4	3	Saucerization		1
tibia	1		Débridement		1
Arthrodesis, foot	9	2	Secondary closure		2
wrist	1		Change of dressing		1
Spinal fusion, long (scoliosis)	6		Operations on tendons	2	4
short		1	Steindler stripping	1	2
Laminectomy	1		Posterior capsulotomy		1
Arthroplasty, hip cup	1		Amputation of digits		2
prosthesis	2		Excision of exostosis	1	
Colonna operation, hip	1		Excision of lipoma	1	
Intramedullary nailing, femur	4		Bunionectomy		2
Internal fixation, hip	3		Meniscectomy	1	3
Open reduction, old fracture	2		Removal loose body, knee		1
Removal of bone plate	1	2	Revision of scar		1
Bone block	1	1	Manipulation		2
Epiphyseal arrest		1	Application of plaster cast		2
	37	10		6	25
			Total	43	35

In those patients in whom major procedures involving bone were performed, the presence of embolic fat was detected in more than 75 per cent, while in those patients undergoing procedures almost entirely confined to the soft tissues, the incidence of detectable fat embolization dropped to less than 20 per cent.

In this group of seventy-eight patients, fat emboli were found in the control blood samples of four. One of these patients was a 79-year-old woman with an intertrochanteric fracture. Ten days after her injury, she was moved from bed and positioned on the operating table before the initial blood sample was obtained. We believe that the positive finding in this control sample was associated with the manipulation of the fracture. In the other three cases, we have no explanation for this finding.

There were no deaths in this group of patients. Among the forty-three patients in whom embolic fat was detected postoperatively, there was only one case in which a severe reaction occurred which might be attributable to fat embolism. The patient was an 8-year-old boy with a congenital dislocation of the hip. Twenty-four hours after an open reduction of the dislocation, his condition suddenly deteriorated. The pulse became very rapid and weak; the skin, moist and cold. The rectal temperature dropped to 97° F.; the systolic blood pressure, to below 100 mm. Hg. His face became gray and ashen with cyanosis of the lips. Abdominal distention appeared rapidly. The patient was supported with intravenous fluids, oxygen, and suction applied to an inlying duodenal tube. Twelve hours later, his condition was more nearly normal, and he had an uneventful convalescence thereafter.

SUMMARY

Previous investigations have visualized embolic fat in the blood of dogs and patients with recent fractures. These droplets ranged in size from 12 to 20 microns in diameter. Similar droplets 7 to 14 microns in diameter have been detected in the circulating blood using a water-soluble fluorochrome, phosphin 3R. This method has been tested in experimental animals with fresh fractures. In each animal in which fractures of the long bones were produced, fat emboli could be found in the peripheral blood. This finding was substantiated in every animal by the detection of fat emboli in sections of tissue removed at autopsy. The presence of alimentary lipemia did not appear to interfere with the application of the method.

In a group of seventy-eight patients undergoing various orthopedic procedures, fat emboli were found in forty-three. There was a good correlation between the magnitude of the bony injury and the presence of embolic fat. Fat emboli were commonly detected following major reconstructive operations upon bone. In frequency of this finding in the absence of clinical signs attributable to fat embolism provokes the speculation that a traumatic lipemia is a normal sequel to bony injury and becomes of pathologic significance only when associated with other factors as yet largely unrecognized.

CONCLUSION

A method for detecting fat emboli in the circulating blood has been developed. This method depends upon the concentration of the emboli by centrifugation and their visualization by fluorescence microscopy after staining

with a water-soluble fluorochrome, phosphin 3R. This method has been used to study the incidence of fat embolism in animals following fractures of the long bones, and in patients undergoing operations of an orthopedic nature.

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RECURRENT GASTRIC CARCINOMA: AN INTERIM EVALUATION OF SURGICAL RESULTS

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MORE than five years have now elapsed since the institution at Memorial Hospital of the program of re-exploration for recurrent gastric cancer. A previous report[7] concerned our early experiences with 7 patients, all of whom were re-explored and 4 of whom were subjected to secondary resection. On the basis of our experience with these 7 patients, we concluded that secondary resections were technically feasible. We proposed in addition that secondary resections of recurrent gastric cancer might afford patients greater comfort and an extended span of life, and might even effect a cure in an occasional case. It is now time to evaluate these hopes in the light of continued experience.

ANALYSIS OF CLINICAL MATERIAL

In addition to the 7 patients originally reported on, 30 more patients have been explored for recurrent gastric cancer in the five-year period, December, 1947, to December, 1952. The indications for re-exploration are identical with those for the primary procedure, namely, clinical or laboratory evidence of localized cancer with no evidence of distant metastasis. There was a preponderance of male patients over female, there being 28 male and 9 female patients, with ages for the entire group of 37 patients ranging from 34 years to 74 years. Of the total of 37 patients who were re-explored for gastric cancer, 15 had secondary resections performed and 22 were found to have recurrent cancer too widely disseminated or too extensive to permit resection. A secondary resectability rate of 40.5 per cent was thus achieved.

Primary Operation.—Of these 37 patients, 15 had the primary resection for gastric cancer performed at Memorial Hospital. The remaining 22 patients had the original operation performed elsewhere, in most instances by surgeons well qualified in the performance of gastric surgery. Thirty patients had had partial or subtotal gastrectomy, 5 had had total gastrectomy, and 2 had had resection of gastric cardia previously performed. It is perhaps of interest to note that only 5 patients previously resected at Memorial Hospital could still be subjected to further potentially curative resection. The remaining 10 previously explored at Memorial Hospital all presented evidence of widely disseminated cancer at the second laparotomy. This is believed due to a more aggressive approach at the time of primary resection on the part of the Memorial surgeons than is frequently practiced by general surgeons elsewhere.

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Interval Betwen Operations.—The average interval between primary and secondary resections in the 15 patients so treated was thirty-three and three-tenths months. By comparison, the time interval between resection and secondary exploration in the 22 secondarily inoperable patients was fourteen and one-tenth months. This difference in interval implies merely that the slower-growing, less aggressive cancer is more amenable to secondary resection than the rapidly growing one. It is of interest to note that, while cancer must have been continuously present in all 37 patients, symptoms indicative of the residual cancer were noted for an average of three and six-tenths months only in 12 of the 15 patients who had secondary resections, and for an average of five and six-tenths months only in the 22 who had secondary exploration only.

This is in accord with the observation of State, Moore, and Wangensteen[16] that following a gastric resection in which cancer is left at the proximal line of resection there is an interval of about fifteen months before the patient has symptoms of recurrence. These authors stated, "This has led us to believe that carcinoma of the stomach may be a silent disease for a period of fifteen to twenty months; and for another four to six months the symptoms may be so vague that the patient fails to seek medical aid."

Secondary Operation.—In 9 of the 15 operable patients, resection of the gastric remnant and lower esophagus in continuity with the spleen and body and tail of the pancreas was the secondary procedure performed. Two of these had resection of the transverse colon as well. One patient, previously subjected to a total gastrectomy, had resection of the esophagojejunal anastomosis, 3 patients had resections of local recurrences which did not involve remaining stomach, and 1 patient had a local resection of most of the gastric remnant, preserving a small rim of fundus. Finally, 1 patient with recurrent cancer in the head of the pancreas and duodenal stump had a pancreatoduodenectomy performed.

Of the 22 inoperable patients, 18 had merely exploratory laparotomy and biopsy. Three had palliative enteroenterostomies performed, and 1 had a palliative resection of gastric remnant performed because incurability was not demonstrated until definitive surgery had thus far been undertaken.

Tertiary Operation.—Five patients in this group of 37 patients were explored a third time. One patient declared locally inoperable by another surgeon at the time of secondary exploration was re-explored by us and incurability was confirmed. Another, although declared locally inoperable elsewhere, was subjected to a third exploration and resection of recurrent cancer successfully accomplished (Fig. 1). Finally, 3 patients were re-explored both a second and a third time at Memorial Hospital, resections being performed at the secondary procedures but only palliative procedures being possible at the last explorations.

Morbidity and Mortality.—Postoperative complications were not too frequent but were seen as often in those undergoing only exploratory laparotomy as in those undergoing extensive resections. Both postoperative fatalities,

however, occurred in elderly patients who had undergone extensive resections. Minor postoperative complications were seen as usual. Those of more importance, and the frequency of their occurrence, are listed in Table I.

There were two surgical deaths in these 37 patients, both occurring in patients who had undergone secondary resections for recurrent gastric cancer. One was a 68-year-old woman who expired on the twenty-fourth postoperative day as a result of empyema, pneumonitis, and cardiac failure. The other was the oldest patient in the series, a 74-year-old man, who expired on the twenty-ninth postoperative day as a result of pancreatic fistula, sepsis, and progressive renal failure. Autopsy was not obtained in either case.

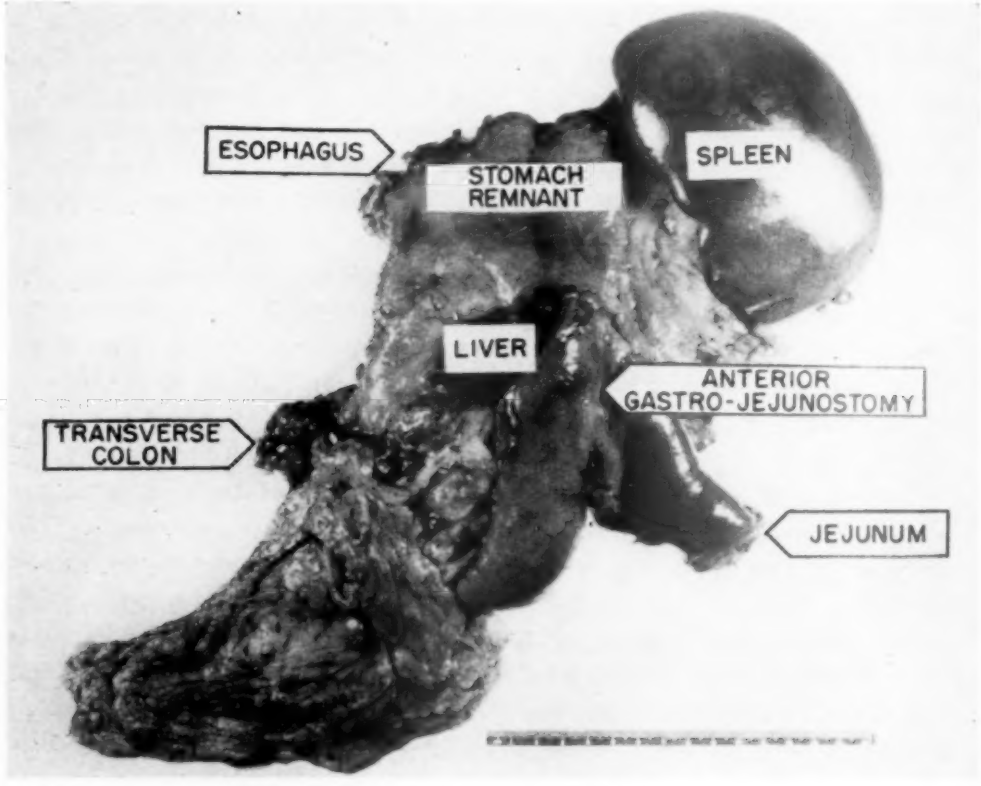

Fig. 1.—Surgical specimen consisting of the remaining stomach, omentum, a portion of transverse colon, distal pancreas, and a small portion of left lobe of liver, which, on pathologic study, showed recurrent adenocarcinoma of stomach extending into anterior and posterior anastomoses and into capsule of liver with metastases to multiple nodes. This patient had the initial resection six and one-half years previously, was re-explored nine months previously because of obstructive symptoms, and an anterior gastroenterostomy was performed in the belief that the recurrent cancer could not be resected. Because of persistent symptoms the patient was referred to Memorial Hospital and this resection was carried out on Dec. 5, 1951. Dissemination of cancer became evident three months following discharge, and the patient died in June, 1952.

Significance of Histologic Grading and Node Metastasis.—It might be anticipated that the highly anaplastic carcinoma would be more likely to disseminate widely than the low-grade carcinoma, and that secondary resection would therefore be possible only in the latter group. Analysis of the histologic grading of the recurrent tumors in the present series is presented in Table II.

Although statistical significance can hardly be derived from so few cases, it would appear that histologic grading was of no great value in anticipating secondary resectability.

TABLE I. RECURRENT GASTRIC CARCINOMA (MEMORIAL HOSPITAL: DECEMBER, 1947–DECEMBER, 1952): POSTOPERATIVE COMPLICATIONS (35 SURVIVING PATIENTS)

Pulmonary	7	
Bronchopneumonia		3
Atelectasis		3
Acute pulmonary edema		1
Wound	5	
Enteric fistula		3
Pancreatic fistula		1
Subhepatic abscess		1
Jaundice	4	
Obstructive		2
Hemolytic		2
Electrolyte imbalance	2	
Pathologic fracture	1	
Prostatic hypertrophy with urinary retention	1	
Thrombophlebitis	1	

TABLE II. RECURRENT GASTRIC CARCINOMA (MEMORIAL HOSPITAL: DECEMBER, 1947–DECEMBER, 1952): HISTOLOGIC GRADING OF TUMORS

TYPE	SECONDARILY RESECTABLE	SECONDARILY INOPERABLE
Adenocarcinoma (unspecified)	4	6
Adenocarcinoma grade II	2	3
Adenocarcinoma grade III	2	7
Anaplastic, gelatinous, or signet-ring carcinoma	4	4
Leiomyosarcoma	3	–
No pathology report available	–	2
Total	15	22

Similarly, the presence or absence of node metastasis at the time of primary resection would seem to have little influence on secondary resectability rate. Information on this matter is available in only 19 of the 37 patients herein presented. Of 12 patients with proved node metastasis at the time of primary surgical resection, 5 were subsequently subjected to secondary resection and 7 were found to be secondarily inoperable. Of 7 patients without node metastasis at the time of primary resection, 2 could be subjected to secondary resection and 5 could not (Table III). This may be compared with the observation of Lewis and Wangensteen[5] in 13 patients whose original gastric resections were for cancer with lymph node metastases and who were re-explored while asymptomatic: Cancer was found in 6 of the 13 patients, and in 5 of these it was possible to resect all of the gross tumor.

TABLE III. RECURRENT GASTRIC CARCINOMA (MEMORIAL HOSPITAL: DECEMBER, 1947–DECEMBER, 1952): NODE METASTASIS AT PRIMARY RESECTION

	SECONDARILY RESECTABLE	SECONDARILY INOPERABLE
Nodes positive	5	7
Nodes negative	2	5

End Results.—All 22 patients who had exploratory laparotomy only, or exploratory laparotomy with some type of palliative procedure, are dead of cancer. Survival in this group from the time of secondary operation to death varied from one month to twenty months, with an average survival of five and seven-tenths months. The patient who survived twenty months was quite comfortable through most of this period. It is doubtful that the exploratory laparotomy materially influenced this apparent palliation. It is certain that the other patients in this group received no significant palliation from the exploration.

Of the 15 patients who had definitive and potentially curative surgery performed, 2 did not survive the postoperative period, as stated previously, and 8 other patients survived from four months to eighteen months before succumbing to disseminated cancer. These 8 patients present an average survival of eight and one-tenth months. There was no great palliation afforded any of these 8 patients but 1, who was completely asymptomatic and comfortable for five months following surgery, but who then developed progressively severe tenesmus and bowel obstruction from massive cul-de-sac metastases and died nine months following surgery.

The remaining 5 patients are living and comfortable, although 2 are known to have metastatic cancer. Both of these latter happen originally to have had gastric leiomyosarcomas. The other 3 patients are living and well without evidence of cancer fifteen months, eighteen months, and five years and ten months, respectively, since the secondary resections. Since the latter patient represents the only apparent "cure" to the present in this series of 37 recurrent gastric carcinomas, a brief résumé of his history is presented.

M. O. (previously reported as Case 2), a 53-year-old elevator operator, had had a partial gastrectomy in another institution on Feb. 20, 1947, for a gastric adenocarcinoma grade III extending close to the proximal line of resection. Convalescence was uneventful and the patient was returned to the care of his local physician. The latter followed the patient regularly by physical examination and, quite ingeniously, by checking for the presence of occult blood in the stool. A positive test for occult blood was first found four months following surgery, and because of its persistence over the next three months, with an associated anemia, and somewhat suggestive findings on gastrointestinal fluoroscopy, the patient was referred to Memorial Hospital for further diagnosis and treatment.

When first seen at Memorial Hospital, the patient was essentially asymptomatic. All physical findings and laboratory studies were normal except that stool specimens were consistently positive for occult blood, even when removed above the hemorrhoidal ring by proctoscope. On the basis of this finding alone, plus a high degree of suspicion that recurrent cancer might be present, the patient was finally explored on Dec. 17, 1947.

An irregular, nodular 3 cm. tumor was palpated in the line of the gastrojejunostomy, but no other evidence of local cancer or distant metastases could be found. Resection of this mass was forthwith undertaken by dividing afferent and efferent loops of jejunum and mobilizing the entire gastric remnant. Total gastrectomy was anticipated, but was not actually performed because of the patient's poor reaction to manipulation of the diaphragm. Instead about 5 per cent of the gastric fundus was retained, and reconstruction was effected after the Roux-en-Y method. The patient's convalescence was complicated by transient hemolytic jaundice but was otherwise uneventful.

Pathologic study of the surgical specimen revealed an adenocarcinoma grade III in the gastrojejunal anastomosis with no evidence of metastasis to lymph nodes of mesentery or omentum.

Since the secondary resection the patient has been followed regularly. Because of signs of an acute surgical abdomen, the patient had laparotomy again performed on Sept. 10, 1948, and an acute gall bladder removed. No cancer was discernible at this operation. The patient has remained consistently well since, and is both economically and socially rehabilitated. He was last examined and found to be in good health on Oct. 21, 1953, almost six years since the secondary resection.

DISCUSSION

In attempting to increase the salvage rate for gastric cancer, two general approaches are available. One seeks an earlier diagnosis of the cancer, and in carrying this to its furthest implications it includes the mass surveys of asymptomatic persons of cancer-bearing age. Reported statistics[13-15] indicate the validity of the observation of Wigh and Swenson that approximately one case of silent gastric cancer can be uncovered in any 1,000 persons over the age of 45 years with sex and age distributions comparable to those of the national population. A higher incidence will be found in the clinical filter methods of State, Gaviser, Hubbard, and Wangensteen,[17] Wangensteen,[2] and Rigler.[12] Of 23 cases of cancer found by such methods, Wigh has predicted a 40 per cent five-year salvage rate. The two cancers, detected at Memorial Hospital during the survey of 2,858 asymptomatic patients, were resected over five years ago and have not recurred, lending support to Wigh's statement. Yet even such noteworthy attempts to reduce cancer mortality by early case finding have not been without severe criticism.[6]

The second general plan of expanding the salvage rate in cancer of the stomach includes all of those surgical procedures designed to increase the efficacy and scope of operation. In this category the present consideration of secondary resection of recurrent gastric cancer is to be evaluated. Resection of recurrent cancer after gastrectomy has been reported only spasmodically. De Amesti[1] in 1949 reported the case of a 35-year-old patient with a recurrence in the esophagojejunal anastomosis fifteen months after total gastrectomy, which he resected successfully seven months after diagnosing the recurrence. Hart[4] has described a remarkable patient who had a partial gastrectomy for cancer in 1943, a total resection, splenectomy, and distal pancreatectomy in March, 1948, for recurrence, and re-exploration over two years later because of troublesome biliary regurgitation with substitution of a "stomachlike pouch" of jejunum. The patient was reported well eighteen months later. Lewis and Wangensteen[5] have reported on 11 patients reoperated upon for recurrent gastric cancer, in 4 of whom it was possible to remove the grossly apparent cancer, 1 dying after leaving the hospital and 2 having nonresectable recurrences at subsequent exploration. Our experience and those elsewhere recorded call to mind the report of Rienhoff[11] concerning Peugniez's patient who had a partial gastrectomy for cancer of the stomach and who at autopsy twenty-five years later, after death from lobar pneumonia, presented retroperitoneal nodal metastases similar to the primary cancer.

Probably of more significance than the occasional cure that may be achieved by secondary resections is the implication from data herein contained that inadequate primary resections are still frequently performed for gastric cancer. Wangensteen and his associates,[19] employing the principle of the "second look," reported their poorest results in gastric cancers exhibiting gross residual tumor (asymptomatic) at the time of elective re-exploration. It is not surprising, therefore, that the prognosis of those explored after symptoms or signs of recurrent cancer have become evident would be equally ominous. In both circumstances, however, the not infrequent finding of grossly resectable cancer would indicate the need for a more extensive and encompassing primary operation.

In a previous communication[8] the inadequacies of partial gastrectomy for the control of cancer have been detailed. Elsewhere, also, the technique of[9] and reason for[18] a more thorough operation for gastric cancer have been described. It would seem that if secondary resection could still be performed in 40.5 per cent of the patients herein reported, a more extensive primary resection not only could have been carried out originally but would possibly have offered these patients a greater chance for cure.

The variation in time of death in these cases is probably explained by the variation in location and extent of metastases. Whether these metastases occurred prior to the first inadequate local resection or during the subsequent long "silent disease"[16] is entirely a matter of conjecture. There is evidence that this silent period is of about the same length whether there are involved lymph nodes at the time of primary resection or not.[3] The surgeon who is critical of his own responsibilities in the management of gastric cancer has nevertheless reason to assume culpability both for local recurrence and for metastasis. Those less willing to indict their surgical judgment can gain ready "surgical absolution" from recurring editorials and papers of surgical philosophical criticism. In our opinion, however, the prophetic utterance of Mullen,[10] which was expressed when the present surgical attack on gastric cancer was first becoming intensified, certainly bears restatement at this time: "It is more important to cast aside meaningless and useless doubts and to dispel the air of pessimism that exists by attempting more thoroughly and skillfully to utilize what is known until better information is available."

CONCLUSIONS

1. While continued experience has confirmed our original opinion that resection of recurrent gastric cancer is often feasible, and while one five-year cure of recurrent gastric cancer has thus been achieved, it would appear that the need for such secondary resections might in large part be obviated by adequate and aggressive primary surgical resection.

2. If a patient is subjected to subtotal gastrectomy for cancer he merits careful anticipatory observation in order to detect recurrence of cancer. It is quite possible that reluctance to re-explore such patients until recurrent cancer is obvious accounts for our many failures, since our only successful secondary resection was re-explored on the basis of minimal indications.

3. End results, from the standpoint of both palliation and cure, in secondary resections for recurrent gastric cancer are so far discouraging. Nevertheless, at the present time it must be conceded that the only alternative to surgical treatment of these patients is complete therapeutic surrender with 100 per cent fatal outcome.

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ACUTE PEPTIC ULCER AS A COMPLICATION OF MAJOR SURGERY, STRESS, OR TRAUMA

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INTRODUCTION

ACUTE peptic ulceration of the upper gastrointestinal tract may be a complication of severe stress or trauma. When this occurs, it can be of more serious consequence than the original disease. Massive hemorrhage or perforation may be present. The purpose of this paper is to discuss this problem briefly, with detailed illustration of two typical cases. In addition, the autopsy material of the Department of Pathology, King County Hospital, Seattle, Washington, was reviewed through the period Jan. 1, 1946, to April 30, 1953, inclusive. Forty-two such cases were found.

The definition of acute ulceration has not been standardized, and it is not always practical or possible to distinguish between acute and chronic peptic ulcers. An attempt has been made to select only those cases in which so-called acute ulcers have formed upon previously normal mucosa during a period of stress. For the purposes of this paper, acute ulceration will be defined as: Shallow ulcers, often multiple, without surrounding induration, and which on microscopic examination do not show evidence of chronic inflammatory response. Not all patients had histologic examination. Those patients who did not were considered satisfactory only if the gross description and the nature of the case was clear cut. Chronic ulcers were included only when there was associated acute ulceration. Ulcers which perforated during the course of other severe illnesses were included if there was no history suggestive of previous chronic ulceration. Those cases in which chronic ulceration was present were considered acceptable only if there was associated acute ulceration. Cases in which perforation followed major surgery, stress, or trauma were considered acceptable for inclusion. All cases were selected from the Department of Pathology records, and such variable evidences as x-ray diagnosis, erosion, edema, or submucosal hemorrhage were not considered valid.

CASE REPORTS

During the period of Jan. 1, 1946, through April 30, 1953, inclusive, 4,102 autopsies were performed. On reviewing these records, acute ulceration was found in forty-two cases. Nine cases were associated with brain damage, six

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cases were associated with major surgery or trauma, and twenty-seven were associated with other diseases. Two of these forty-two cases will be presented in detail. The remaining will be presented in an abbreviated form in Table I.

CASE 1.—A young man expired five days following a compound fracture of the left femur and associated injuries. Perforation of an acute duodenal ulcer with peritonitis was found at autopsy.

Clinical History.—A 30-year-old white man, previously in excellent health, was injured in an automobile accident on Dec. 9, 1952. On admission to the hospital shortly thereafter, his blood pressure was unobtainable, and he was pale with cold, moist skin. There was an obvious compound fracture of the left tibia and fibula, with laceration of the popliteal space, and no detectable pulsations in the arteries of the lower extremity.

Treatment.—The patient received 1,000 c.c. of blood intravenously, and had sterile preparation of the left lower extremity. At the onset of surgery, the blood pressure was 130/80 mm. Hg, and the pulse 100 and regular. He was alert, talking, and reasonably comfortable.

Operative Procedure.—The patient's induction anesthetic was Pentothal Sodium. By means of an endotracheal tube, nitrous oxide, ether, and oxygen were administered. Initial débridement was performed by the orthopedic department, at which time it was found that the femoral artery had been completely severed at its distal one-third, and a recent clot in the proximal vessel prevented further bleeding. A vascular surgeon was called. The vessel was freed and anastomosed with 000000 black silk, using an everting type suture. The surgeon was able to demonstrate re-established circulation at the end of the procedure. Following this, the orthopedic department performed an open reduction and internal fixation of the distal one-third of the femur. A Steinmann pin was placed through the distal one-third of the tibia and fibula for traction fixation and immobilization. At the end of surgery, the circulation of the lower extremity was in doubt. Peripheral pulsations could not be identified, and the extremity was cold and cyanotic. One cubic centimeter of $\frac{1}{1000}$ histamine phosphate in 100 c.c. of normal saline solution was injected into the femoral artery. No appreciable effect was recorded. Additional data include: length of anesthesia, seven hours; average blood pressure during surgery, 110/70 to 140/80; pulse, 100 and steady; fluids, 2,500 c.c. blood; 1,500 c.c. dextrose in water; and condition at close of surgery, satisfactory.

Postoperative Course.—The first postoperative day, the patient's temperature varied between 101° and 102° F. He excreted approximately 400 c.c. of clear urine. Blood pressure remained approximately 120/70 and pulse about 100. The patient was inadvertently given 200 mg. of heparin intramuscularly following surgery, and bled rather profusely from the operative site during the next twelve hours. He received 2,000 c.c. of intravenous fluids, and 25 mg. of Priscoline intramuscularly every four hours. The left lower extremity remained cold and somewhat cyanotic. Toward the end of the day, 10 c.c. of 2 per cent procaine was injected into the femoral artery with questionable improvement. In addition, a lumbar sympathetic block was performed. An emesis of 800 c.c. was recorded, which was coffee ground in nature and guaiac positive.

During the following twenty-four hours, the circulation of the left lower extremity continued to be impaired. The patient had another 600 c.c. coffee-ground, guaiac-positive emesis, and complained of epigastric pain. A Levin tube was inserted, and the patient was placed on constant suction. The blood pressure remained steady at 120/70, but the pulse rate increased to between 120 and 130. During the first part of the day, the patient received 500 c.c. of saline solution and 500 c.c. of 10 per cent dextrose and water. Toward the end of the day, his blood pressure fell to 60/40, his skin was cold and clammy, and his pulse thready. This state of shock was unexplained at the time. After the patient was given 1,500 c.c. of blood, the shock state responded, and the blood pressure returned to 120/70. During this time, approximately 2,700 c.c. of gastric suction was recorded, and he excreted

480 c.c. of urine. His temperature remained at 102° F. or above. Laboratory work returned from the previous day showed: blood urea nitrogen 69, CO_2 21, chlorides 96, sodium 142, and potassium 4.1.

On the third day it was obvious that the patient's general condition was deteriorating. He received 3,000 c.c. of dextrose and water, 1,000 c.c. blood, and 20 meq. of potassium chloride in 500 c.c. of dextrose and water. Gastric suction for the day, including emesis about the Levin tube, was approximately 3,850 c.c., and the urine output was 200 c.c. His CO_2 was 31, and chlorides were 74. Pulse was 130, blood pressure 100/70, and temperature 103° F. and above.

The patient's condition was critical on the fourth postoperative day. The initial hematocrit of 40 had fallen to 30, the CO_2 was 33, chlorides 68, sodium 146, potassium 6.5, and blood urea nitrogen 128. The urinary output was negligible. The patient was cyanotic, comatose, and had labored respiration. The gastric aspirations were strongly guaiac positive. The chest was clear to auscultation and percussion, and the heart sounds were somewhat obscured. There were occasional high-pitched bowel tones, but the abdomen was generally silent. On palpation, there was some question of peritoneal irritation. Needle aspiration of the abdomen yielded a bile-stained fluid with a pH of 7.4 as opposed to a pH of 2.0 for the gastric suction. It was felt that the aspirating needle might have entered a loop of bowel. The possibility of a perforated viscus was entertained, but the general condition of the patient had deteriorated to the point that surgery was not thought feasible. An intravenous solution of ammonium chloride was begun in an attempt to correct the chloride deficit. The total intake for the day was 500 c.c. of blood, 2,000 c.c. of dextrose and water, 600 c.c. of dextrose and saline solution, and 500 c.c. of 0.9 per cent ammonium chloride solution. The total output was 2,500 c.c. by gastric suction, which was coffee ground in nature and guaiac positive. The patient became moribund on the following day and died during that morning.

Autopsy Findings.—At autopsy there was evidence of generalized peritonitis, with a large perforation of the first portion of the duodenum, approximately 3 by 2 cm. The edges were somewhat indurated and irregular. The lower lobes of both lungs showed hyperemia and edema. There was a thrombosis of the left femoral artery at the site of the anastomosis. The kidneys were not remarkable grossly, but on microscopic examination there was evidence of lower nephron nephrosis.

CASE 2.—The second case is that of a 72-year-old white woman who sustained 65 per cent second and third degree burns, and who died five days later. At autopsy there was found a posterior perforation of the duodenum and peritonitis of the lesser peritoneal space.

Clinical History.—A 72-year-old white woman sustained severe burns of the body when her clothing caught on fire. On admission to King County Hospital Nov. 27, 1952, her blood pressure was 140/80, pulse 100 and irregular, lungs clear, and her heart enlarged to the anterior axillary line with a systolic murmur over the aortic area. Reflexes were within normal limits. There was an estimated 65 per cent total burn surface, of which 25 per cent was third degree, and centered mostly about the perineum and the right thigh. The remaining burned area, approximately 40 per cent of the body surface, included both arms, both legs, both sides of the trunk, and extended onto the face and neck.

Treatment.—The patient was taken to surgery immediately, and the exposure type of burn therapy was instituted, the patient being placed on sterile towels and on a sterile sheet. The plan of fluid therapy was calculated on the basis of a 70-kilogram patient with a 65 per cent burned area, an estimated 3,000 c.c. of saline solution and 3,000 c.c. of blood, with an optional 2,000 c.c. of dextrose and water to be given intravenously in the first twenty-four hours. Initial laboratory work revealed the hematocrit to be 49 and the urinalysis normal.

During the first twenty-four hours, the patient received 2,000 c.c. of blood, 4,000 c.c. dextrose and saline solution, and 2,500 c.c. dextrose and water. Her twenty-four-hour urinary output was 440 c.c. At the end of this time, hematocrit was 55, chlorides 98, and sodium 147. Daily intravenous administration of 500 mg. of Terramycin was begun.

During the second day, the patient's hematocrit rose to 67.5 and 77 on two readings. The patient was given 3,000 c.c. dextrose and water and 1,000 c.c. dextrose and saline solution.

Oral intake was 2,100 c.c. The total urinary output for the second day was 580 c.c. Her temperature during the second twenty-four hours rose to 100.8° F., and her pulse remained between 100 and 110.

On the third day, the hematocrit varied between 56 and 48. The patient received 1,000 c.c. dextrose and water, 2,800 c.c. oral fluids, and 1,000 c.c. plasma. Urinary output during this time was 600 c.c. The patient complained of rather severe epigastric burning pain, and Amphojel was given with some clinical relief.

On the following day, the hematocrit was 48, blood urea nitrogen 39.3, CO_2 23, chlorides 99, sodium 142, and potassium 3.9. The patient received 3,250 c.c. dextrose and water intravenously, and approximately 2,400 c.c. orally. The urinary output was 500 c.c. Toward the end of the fourth day, the patient began vomiting small amounts of coffee-ground, guaiac-positive fluid.

On the patient's fifth and last hospital day, her condition was critical. There was evidence, by physical and x-ray examination of the chest, of increased heart size and pulmonary congestion. The electrocardiogram showed auricular fibrillation. Her temperature remained above 100° F., and she was somnolent and semicomatose. During the day she received 3,000 c.c. dextrose and water and 1,000 c.c. dextrose and saline solution with 40 meq. potassium chloride. Laboratory reports on that day showed CO_2 23, chlorides 95, sodium 135, potassium 3.7, hematocrit 51, and white blood count 5,300. During a bed change, the patient vomited approximately 1,000 c.c. of dark brown coffee-ground fluid, and died shortly thereafter.

Autopsy Findings.—At autopsy there was a posterior perforation, approximately 1.5 cm. in diameter, in the second portion of the duodenum, with lesser sac peritonitis, right and left lower lobe bronchopneumonia, and myocardial fibrosis.

ANALYSIS OF CASES

The additional forty cases are listed in Table I. A photograph of a representative ulcer (Case 39) and photomicrographs of two typical ulcers (Cases 38 and 40) are shown in Figs. 1 through 3. It was surprising to us, when we reviewed the case records, how many cases of acute ulcer there were in the type of patient under consideration. Associated massive hemorrhage or perforation tended to render the ulcer more important than the original provoking condition. There were at least nine instances of perforation and at least six cases of massive hemorrhage. (In Case 13, included in these figures, both perforation and massive hemorrhage occurred.) In every case there was coffee-ground material, and in a number of instances the stomach contained a considerable quantity of dark purple clot.

The patients varied in age from 30 to 84 years, the average being 62 years. In our series, such secondary acute ulceration was slightly over two times more common in the men than in the women. The problem of seasonal variation and ulcer formation has been cited in connection with ordinary primary chronic peptic ulcers in the literature on several occasions. In this series, the monthly incidence of occurrence of the acute ulcers, January to December inclusive, was 4, 4, 4, 8, 4, 4, 2, 1, 3, 0, 4, and 4, respectively.* The low incidence in the four months comprising the summer and early autumn (July to October), six cases (14 per cent of cases) (four months equals 33 per cent of time), is of some interest.

In general, our series would support the view that there is a correlation between the severity of the original disease and the likelihood of secondary acute

*It should be remembered that since the series ended April 30, 1953, the first four months of the year are represented eight times, the others only seven.

TABLE I. ABBREVIATED DATA CONCERNING FORTY ADDITIONAL CASES OF ACUTE ULCER FOUND AT AUTOPSY (THE OTHER TWO CASES ARE COVERED BY THE COMPLETE CASE REPORTS)

	PATIENT	AGE (YR.)	SEX	ASSOCIATED DISEASE(S)	AUTOPSY FINDINGS
3	T. P.	70	M	Cerebral vascular accident; bronchopneumonia	Two shallow 1 cm. ulcerations of the stomach with rounded flat edges; 1 shallow 0.5 cm. ulcer adjacent to pyloric ring in the duodenum with smooth rounded edge; microscopic: acute ulceration, stomach and duodenum
4	L. M. G.	54	F	Cerebral vascular accident (C. V. A.)	Perforation, lesser curvature of stomach, adjacent to the pylorus; the ulcer crater was 1 cm. in diameter; there was a smaller, 0.8 cm. crater on the anterior surface of the greater curvature, also adjacent to the pylorus
5	H. W. S.	40	M	Fractured skull, with subarachnoid hemorrhage	One cm. crater, extending through mucosa and into muscularis layer with sharp edges and no induration located in the stomach adjacent to pylorus; microscopic: acute ulcer
6	E. H.	76	F	C. V. A.	Multiple acute ulcers, stomach
7	A. B.	74	M	C. V. A.	Perforation of the lesser curvature of the stomach just distal to the pylorus, measuring 0.8 cm.
8	E. E. H.	32	M	C. V. A.	Small superficial regions of ulceration both on gross and microscopic examination of the duodenum
9	J. L. O.	57	M	Subarachnoid hemorrhage	Shallow crater in the first portion of the duodenum, measuring 1.3 cm. with red overhanging mucosal margins and only slight thickening of the adjacent wall
10	W. L. T.	53	M	C. V. A.	Shallow crater, lesser curvature of stomach, with clearly demarcated and slightly overhanging margin which was not indurated or elevated; its center contained soft, black material
11	B. L. V.	68	F	C. V. A.	Acute gastric ulcer
12	A. D. R.	47	F	Postoperative: death, following gastrojejunostomy	Acute ulceration at the gastrojejunal anastomosis
13	C. W. W.	66	M	Right inguinal herniorrhaphy, followed by perforation of duodenum 1 day postoperatively; this was surgically closed; patient died of massive gastrointestinal hemorrhage 20 days later	There was an ulcer crater which extended almost completely around the duodenum, just beyond the pylorus; its margins were well punched out; there was no increased thickening of the margin of the ulceration
14	R. P.	65	M	Congestive heart failure	0.3 cm. perforation, first portion duodenum; moderate surrounding induration; 2 additional small shallow ulcerations, 5 cm. from the pylorus; edges of these ulcers showed moderate reddening and induration
15	J. T.	56	M	Chronic emphysema	Crescent-shaped ulceration, second portion duodenum, 2 cm. in diameter; slightly indurated; base contained dark purple clot; microscopic: acute ulcer

16	A. M.	51	F	Cardiac decompensation	In the prepyloric region on the posterior wall, 2 ulcer craters 1.5 cm. in diameter; just distal to the pyloric ring on the duodenal side, 2 additional sharply demarcated ulcers, 1 cm. in diameter; microscopic: details of chronic inflammation without fibrosis
17	A. D. H.	83	M	Generalized peritonitis	1 cm. perforation first portion of the duodenum; mucosal margins were soft and friable, corresponding to an acute ulceration with perforation
18	W. B.	43	M	Severe alcoholism	1 cm. perforation anterior surface first portion of the duodenum, with sharply demarcated mucosal defect and overhanging mucosal margins; no discoloration or induration; adjacent to the perforation there was an additional shallow ulcer, 0.4 cm. in depth, with soft mucosal margins; there were 2 additional similar acute ulcerations just distal to the perforation
19	S. H. T.	82	F	Arteriosclerotic heart disease	Chronic ulcer, prepyloric, and associated shallow ulcer crater 1 cm. in diameter; in addition, there were 2 small shallow ulcers just proximal to the pyloric ring, and an additional shallow ulcer just distal to the pyloric ring
20	P. T. E.	48	M	Chronic alcoholism	The mucosal surfaces of the prepyloric region of the stomach and of the duodenum were broken by multiple shallow ulcer craters; the centers of some contained firmly adherent dark black clots; microscopic: acute ulcerations
21	E. J. P.	63	M	Diabetes mellitus	Chronic ulcer, prepyloric, associated shallow ulcer just distal to the pyloric ring along the lesser curvature, 1 cm. in diameter, with moderate surrounding induration
22	B. M. R.	70	F	Cirrhosis of liver	Multiple 0.4 cm. superficial ulceration, prepyloric; chronic ulceration first portion duodenum
23	Y. K.	66	M	Carcinoma of liver	Over the entire mucosal surface of the stomach, from the cardia to the pyloric ring, were innumerable shallow ulcerations, the edges of which were smooth and rounded; the craters varied from pin point to 1.5 cm. in diameter; many contained dark purple clots
24	F. P.	70	M	Pulmonary tuberculosis	On the posterior aspect of the lesser curvature, prepyloric, were four shallow, sharply demarcated craters, the smallest being 0.5 cm; there was no induration of the surrounding mucosa; in the first portion of the duodenum there was a chronic ulcer with surrounding induration
25	R. T.	63	M	Primary carcinoma of liver	Shallow ulceration greater curvature, prepyloric, compatible with acute ulcer
26	A. J. M.	75	M	Lobar pneumonia	The stomach contained approximately ten 0.4 cm. superficial ulcerations, with slightly raised edges; microscopic: acute ulcers
27	A. E. R.	80	F	Arteriosclerotic heart disease	Multiple acute ulcerations of the stomach

TABLE I—CONT'D

	PATIENT	AGE (YR.)	SEX	ASSOCIATED DISEASE(S)	AUTOPSY FINDINGS
28	C. W.	77	F	Coronary occlusion	Superficial ulceration, lesser curvature stomach; microscopic: compatible with acute ulcer
29	J. M.	62	M	Massive gastrointestinal hemorrhage	In the lower portion of the esophagus at the junction with the stomach there was a ridgelike elevation, 0.5 cm. by 2.5 cm., with red-purple eroded center; microscopic: superficial ulceration eroding into esophageal varix
30	H. P.	81	M	Hypertensive cardiovascular disease	There was a 2 by 3 cm. shallow ulcer along the lesser curvature of the stomach, filled with clotted blood; its edges were flat and not indurated, and there was no undermining; microscopic: acute ulcer
31	H. J.	72	M	Chronic coronary insufficiency	In the prepyloric area there was a 0.5 cm. shallow ulceration, with slightly raised edges, compatible with acute ulcer
32	P. J. M.	73	F	Coronary occlusion	The stomach contained 4 shallow ulcerations, 1 to 1.5 cm. in diameter, with dark reddish bases, and slightly rolled margins; microscopic: acute ulcers
33	T. D.	69	M	Cardiac decompensation	The mucosa of the stomach contained 3 shallow ulcer craters in the prepyloric region. The largest was 1.5 by 2 cm.; the craters were smooth, and their margins were soft and flat
34	E. A.	62	M	Peritonitis from perforated bladder diverticulum	The stomach was distended with dark purple clotted blood; there were 4 shallow ulcers in the prepyloric region, all of which had a dark red base, with smooth edges, and little or no surrounding induration
35	R. P.	83	M	Hypertensive cardiovascular disease	Ulcer of the duodenum compatible with acute superficial ulcer
36	C. L.	72	M	Acute myocardial infarct	Small acute ulcer of the distal stomach
37	A. H.	55	M	Hypertensive cardiovascular disease	On the posterior surface of the duodenum, 5 cm. from the pylorus, was a superficial shallow ulceration without evidence of induration of the surrounding tissue
38	H. S.	64	M	Chronic pulmonary emphysema	Throughout the stomach there were multiple small ulcerations varying from 0.2 cm. to 1 cm. in diameter; many of these contained dark purple clots; the mucosa surrounding them was only slightly indurated
39	M. P.	28	F	Poliomyelitis, bulbar	A crescent-shaped ulcer of the first portion of the duodenum 3 cm. long with soft borders, shallow with slightly elevated margins, and filled with dark purple clot; microscopic: acute ulcer
40	R. W.	69	M	Diabetes mellitus with arteriosclerotic heart disease	Prepyloric 1 cm. diameter shallow ulcer crater with soft slightly rolled edges; ulcer down to, but not through, muscularis
41	C. N.	84	M	Cervical jejunostomy; carcinoma of esophagus; jejunoplasty 14 days before death; drainage abdominal abscess 1 day before death	Perforated duodenal ulcer 2.5 cm. distal to pylorus, adherent to liver; microscopic: acute ulcer
42	L. S.	46	F	Carcinoma of cervix	Shallow 1 by 2 cm. ulcer on posterior surface of duodenum adjacent to pylorus; margins slightly indurated; microscopic: acute ulcer

ulcer formation, but this is very difficult to prove. In the clinical records reviewed, there is often a variation in the observations of the different attending physicians concerning the severity of the illness. Furthermore, it is difficult to correlate the onset of symptoms which would be suggestive of the development of secondary acute ulcers and their presence at the autopsy table.

For the purposes of this paper it will be assumed that acute ulcerations of the upper gastrointestinal tract are preceded by increased hydrochloric acid and pepsin concentrations in the stomach.[1-3] Other mechanisms cannot be entirely ruled out.[4] Acute ulceration of the upper gastrointestinal tract is often associated with brain damage. The central nervous system plays a paramount role in gastrointestinal physiology. There are three types of central response, the parasympathetic, sympathetic, and humoral, all of which originate in the hypothalamus or pituitary gland.[6]

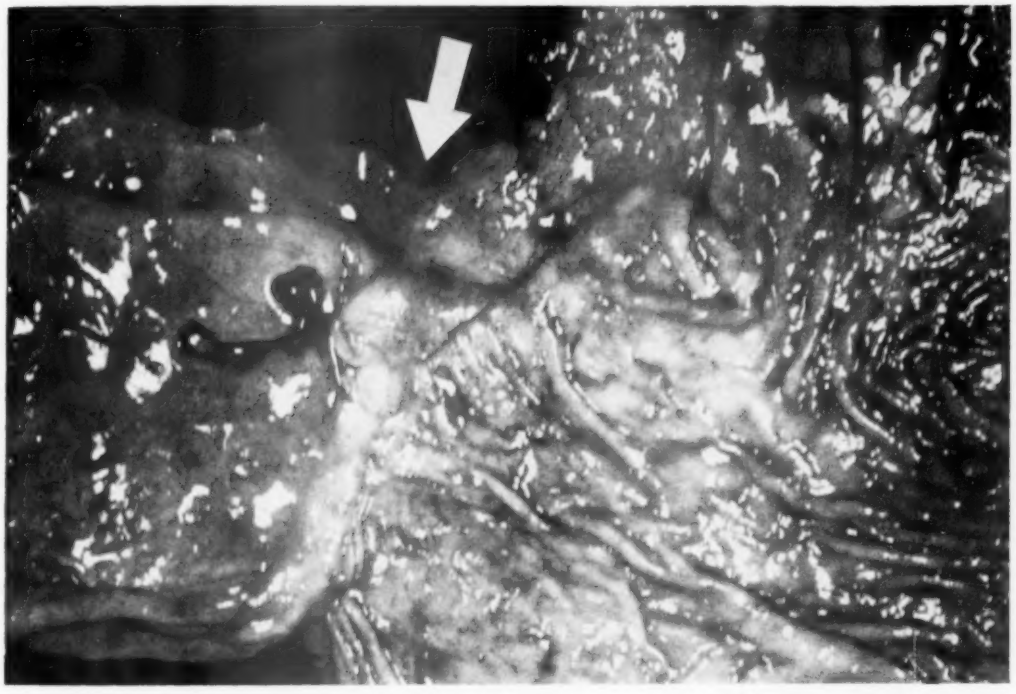


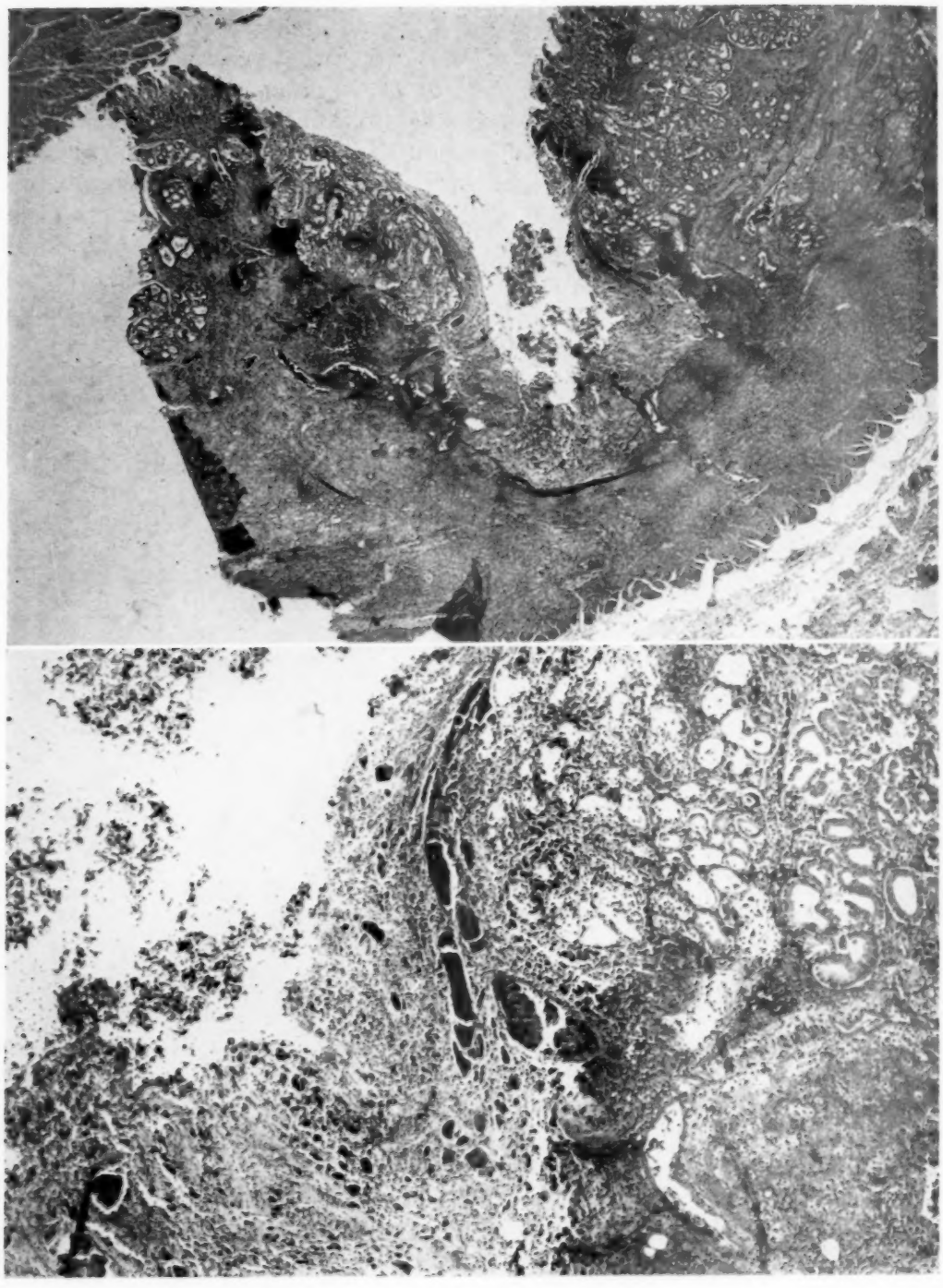
Fig. 1.—Typical acute duodenal ulcer (Case 39). The arrow shows the pyloric ring.

The parasympathetic response is mediated through the vagus nerve. Stimulation of this nerve increases motility, basal secretion, and hydrochloric acid and pepsin production in the stomach.

The sympathetic response generally tends to decrease motility, and to control the diameter of the rich submucosal vascular bed present in the upper gastrointestinal tract. Under certain conditions, this response may increase susceptibility to ulceration through local ischemia.

The humoral concept is somewhat more recent.[7] There is evidence that excessive amounts of ACTH released by the anterior pituitary gland, and the subsequent overproduction of adrenalcortical hormone, cause increased basal

A.



B.

Fig. 2.—Microscopic section of acute gastric ulcer (Case 38). *A*, Low-power view (×8; reduced ¼) and *B*, high-power view (×50, reduced ¼) of portion of ulcer, showing thrombosis in blood vessels.

secretion and increased hydrochloric acid and pepsin production.[8, 9] If the pituitary gland is severed from the hypothalamus, then hypothalamic stimulation will continue to cause ACTH production.[5] This indicates a possible humoral pathway. Some workers have prepared extracts of the hypothalamus which will stimulate the anterior pituitary gland in the same manner.[7] Cushing,[10] in 1932,

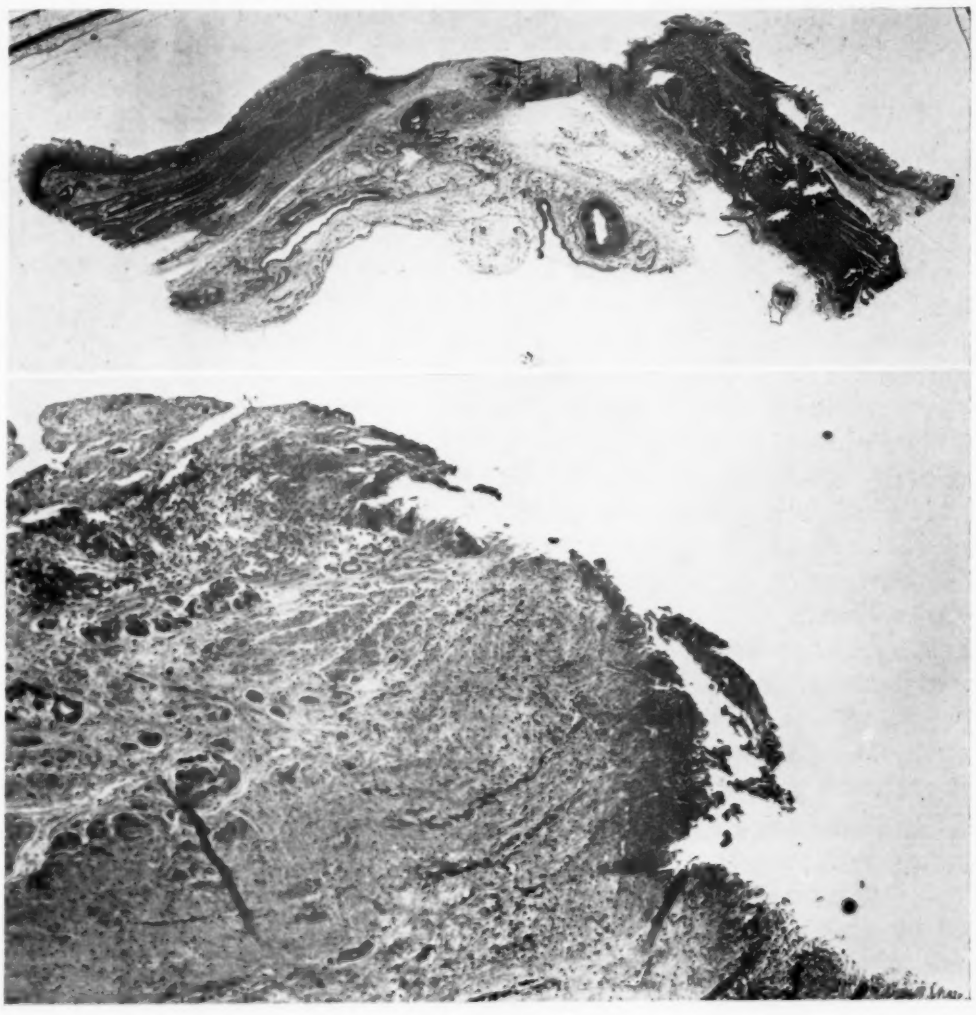


Fig. 3.—Microscopic section of acute prepyloric ulcer (Case 40). *A*, Low-power view (×4; reduced ¼) and *B*, high-power view (×60; reduced ¼) of left margin of ulcer. This ulcer is somewhat more acute than that shown in Fig. 2.

showed that lesions of the hypothalamus are occasionally associated with gastrointestinal ulceration. Other workers have submitted evidence that ulceration occurs in a variety of patients, associated with generalized central nervous system damage.[11] In these patients, discrete lesions of the hypothalamus are often not identified. These workers suggested that anoxia and edema accompanying

any insult to the central nervous system may stimulate the hypothalamus. It is generally believed that the mechanism of ulceration by this manner is through vagal stimulation.[1, 11] Zubiran[12] demonstrated hypersecretion of gastric juice and increased free acid concentration in Heidenhain pouch dogs with and without vagal innervation, during cortisone administration. He also found in animals with isolated stomach pouches, where the antrum had been extirpated, that administration of cortisone caused increased hydrochloric acid secretion. He also stated that in a series of vagotomies in patients for chronic peptic ulcer, approximately 98 per cent had normal levels of hydrochloric acid following complete vagotomy. Selye,[13] in his article on the adaptation syndrome, indicated that numerous nonspecific stimuli may cause acute ulcerations similar to those produced with overdosage of ACTH or cortisone. He and others have indicated that purely emotional stimuli in man will cause acute ulceration.[14]

The hypothalamus plays an unusually important role in gastrointestinal physiology.[15] It is the center of the emotional response. It is intimately associated with the pituitary gland, directly through its neural stock, and perhaps indirectly by humoral pathways.[7] It has been indicated that under ordinary conditions in the normal human being, the hypothalamus is relatively insensitive to such stimulus as epinephrine.[16] However, during disease states, such as Cushing's disease, or with injury to the central nervous system, it may be unusually sensitive.[17] Thorn and his associates [18] stated that the epinephrine test is a satisfactory measure of adrenal-cortical activity in patients with normal hypothalamic and pituitary function.[14] They and others[19-21] have indicated that increased 11-17 corticosteroids and potassium excretion in the urine are correlated with corticosteroid production. Spiro[22] and others[23-26] have studied the effects of cortisone and ACTH on uropepsin excretion in the urine. They have demonstrated that it is a direct measure of pepsinogen production. In patients with chronic ulcers, it is excreted in amounts greater than those found in normal persons. Administration of ACTH or cortisone to a normal person may raise the uropepsin level until it corresponds with that seen in ulcer patients.

In those patients who have come to autopsy following major surgery, severe burns, or trauma, acute ulcerations are occasionally found.[27] Harkins (1938, 1947)[28,29] reported a 3.8 per cent incidence of Curling's ulcer in a series of 680 patients who died following extensive burns. He indicated that patients with infected or unusually extensive burns were more susceptible to ulceration. McDonnell and McCloskey[30] have found a 3.24 per cent incidence of acute ulceration in 243 postsurgical deaths. There may be some correlation between the severity of the disease process and acute ulceration. For example, Bulger and Northrop[31] have reported a 22-month-old infant girl who, as a result of snake bite, developed an unusually severe central nervous system reaction. This was manifested by hyperexcitability and convulsive movements. This infant developed a perforated duodenal ulcer on the fourth day. McDonnell and McCloskey[30] have also reported five cases of activation of chronic ulcers, or formation of acute ulceration, immediately following surgery. In a recent editorial, Dragstedt[32] (1953) postulated that there are two mechanisms whereby

stress can cause peptic ulceration. Minor stresses may act by way of the vagal nervous pathways, while severe stress may cause a release of corticotrophin, with its secondary effect of augmenting the output of cortisone from the adrenal glands. Speaking of this second mechanism, he stated that the occurrence of peptic ulceration after severe burns and "other serious traumas could be dependent upon this mechanism since there is better evidence that these severe bodily stresses excite the adrenal mechanism."

Friesen[33] (1950), in an excellent review with experimental studies, demonstrated the importance of hemoconcentrations in the etiology of peptic ulceration following burns. He showed that there exists a direct relationship between the occurrence of gastrointestinal congestion and hemoconcentration. Treatment of the hemoconcentration prevented the gastrointestinal congestion which is the prelude to ulceration. Friesen concluded: "Gastroduodenal ulceration occurs only in those animals in which hemoconcentration, with its resultant mucosal congestion, attends the burn, and is not seen when hemoconcentration fails to develop." Lillehei, Roth, and Wangensteen[34] (1951) extended this hypothesis to show "that a number of stress provoking agencies in experimental animals fail to influence gastric secretion or even depress gastric acidity; but nevertheless, they exert a powerful ulcer abetting effect by reducing the resistance of the gastroduodenal mucosa to autodigestion." These authors cited ten patients who developed severe peptic ulcer disease for the first time as the result of the stress of a surgical operation or the administration of ACTH or cortisone. Salasin and Bowers[35] (1953) reported an instance of hemorrhage from stress ulcer successfully treated by gastric resection.

Weigel, Artz, Reiss, Davis, and Amspacher[36] (1953) made a significant contribution to the clinical study of Curling's ulcer following burns. In a series of twenty-seven deaths on their very large burn service at Brooke Army Hospital, autopsy revealed seven instances of gastrointestinal ulceration (26 per cent). This incidence is much higher than in some previous reports.[29] "This high incidence is evidence against the general impression that gastrointestinal ulcers after burns are less common . . . than they were formerly." In addition, these authors collected seventeen cases of Curling's ulcer reported in the literature since 1942. In the entire series of twenty-four cases, including multiple lesions, twenty were in the duodenum, nine in the stomach, five in the esophagus, and one in the terminal ileum. The instance of one of the esophageal ulcers and of the ulcer in the terminal ileum, both reported in the German literature, might not be acceptable to all surgeons as representing true instances of Curling's ulcer. In twenty-two of the cases with data available, hemorrhage occurred in ten, and perforation in seven. These Army authors also pointed out that hemorrhage usually occurred on the eighth to the tenth day and perforation on the thirtieth day. They suggested that "an emergency operation may be indicated when a massive gastrointestinal hemorrhage occurs after burns."

Acute ulceration is often seen at autopsy associated with a variety of medical diseases. Many times its presence was not suspected by the clinician.

The tendency is to treat what may be considered the main disease process, that is, coronary thrombosis. A certain percentage of these patients come to autopsy as a result of hemorrhage or perforation of an acute ulcer.

Since the advent of ACTH and cortisone, and the extensive treatment of various diseases with these drugs, there have been numerous case reports in the literature[37-41] of activation of chronic ulcers or formation of acute ulcers, many of which have bled massively or have perforated. The onset of symptoms may occur at a variable time after the administration of these drugs. In some cases, activation has occurred within days or weeks, whereas in others the drug may have been administered for months before gastrointestinal symptoms appeared.

In this presentation, an attempt has been made not to include any ulcers which are on a post-mortem erosion basis. The discrete nature of many of the ulcers is evidence that this attempt has been reasonably successful.

SUMMARY

Forty-two cases of acute ulceration have been reported which developed during the course of other acute illnesses. The possible mechanisms of development of such secondary ulceration are discussed.

ADDENDUM

Since the writing of this paper, an excellent article by Mears[43] (1953) has appeared. This paper approaches the subject from a slightly different angle, but comes to the same general conclusion concerning the frequency of acute peptic ulcer in association with certain other causes of death as does this paper. Mears found thirty-two instances of ulcer in 1,000 unselected consecutive control autopsies at the University of Minnesota in which the ulcer was not the cause of death (3.2 per cent). The incidence of ulcer in separate series of selected autopsies in which the primary cause of death was certain special predisposing conditions is as follows: burns, 1.9 per cent (3.8 per cent if hemorrhagic erosions are included); coronary occlusion, 7.7 per cent; hypertensive heart disease, 4.3 per cent; fractures of the long bones, 2.2 per cent; and chronic ulcerative colitis, 4.3 per cent. A total of thirty-three instances of ulcer is included in these special series. In several instances these figures are definitely greater than the control value in the 1,000 consecutive autopsies of 3.2 per cent. This difference is accentuated when it is pointed out that all of the ulcers in Mears's burns and fracture series were acute ulcers. Nine of thirteen cases in the coronary occlusion series were acute. A differentiation between acute and chronic ulcer is not always made in the other special series, or in the control series. Of the thirty-three instances of ulcer in Mears's special series, fifteen were gastric, sixteen duodenal, and two both gastric and duodenal. In our series of forty-two instances of acute ulcer, twenty were gastric, fourteen duodenal, six both gastric and duodenal, one gastrojejunal, and one (Case 29) an instance of esophageal ulcer involving superficial erosion of an esophageal varix.[44-46]

CONCLUSIONS

1. The syndrome of secondary acute peptic ulceration is much more common than we had realized (1 per cent incidence in 4,102 autopsies).

2. Such ulcers may occur following a number of primary conditions, including major surgery, stress, or trauma, and not just after burns, as was formerly believed.

3. The nature of the primary conditions usually includes an element of stress, so that a possible mechanism of production of the ulcers involves, as a final pathway, the action of an adrenal cortical hormone on the stomach, increasing gastric secretion.

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THE INFLUENCE OF SUTURE METHOD UPON THE INCIDENCE OF THROMBOSIS IN ARTERY-ARTERY, VEIN-VEIN, AND ARTERY-VEIN-ARTERY ANASTOMOSES

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HOW should a severed blood vessel be repaired? Should the everting mattress or the end-on coaptation suture method be employed (Fig. 1)? Despite extensive experimental vascular surgery experience, we did not know this answer. The following experiments were performed to answer this question.

EXPERIMENTAL METHOD

In order to ensure a controlled study, paired blood vessels were severed and then repaired in the same animal. The right vessel was repaired using the continuous everting mattress suture method, while the left vessel was repaired using the continuous end-on coaptation suture method. Thus, the two suture methods were biologically controlled. Variations in technique were controlled by having each author operate upon one-half of the animals and by having paired vessels performed by the same operator.

Artery-artery, vein-vein, and artery-vein-artery anastomoses were performed by the everting mattress technique on the right paired vessel and by the end-on coaptation technique on the left. Glover or Potts vascular clamps were employed to occlude the vessels during performance of the anastomoses. Arterial silk suture, 00000, was used in all experiments. Sufficient adventitia was removed to prevent its being pulled into the lumen of the vessel by the stitches during the anastomoses. The distance of the bites from the vessel edge varied from 0.5 to 1.0 mm. The stitches were placed about 1 mm. apart in most instances. After completion of the anastomoses, careful measurements were taken of each anastomosis and of the vessel or graft above and below each anastomosis.

All animals were given 300,000 units of penicillin intramuscularly during each of the first five postoperative days. No other special care was given. Anticoagulants were not used. After six weeks, each dog was anesthetized. The wounds were opened and the anastomoses inspected. The measurements previously taken were repeated, and the anastomosed vessels removed. Excised segments containing the anastomoses were then opened and the gross characteristics noted.

Artery-Artery Anastomoses.—In twenty-five dogs under Nembutal anesthesia, 100 anastomoses were performed. In each dog, both carotid arteries and both femoral arteries were divided and then repaired. The everting

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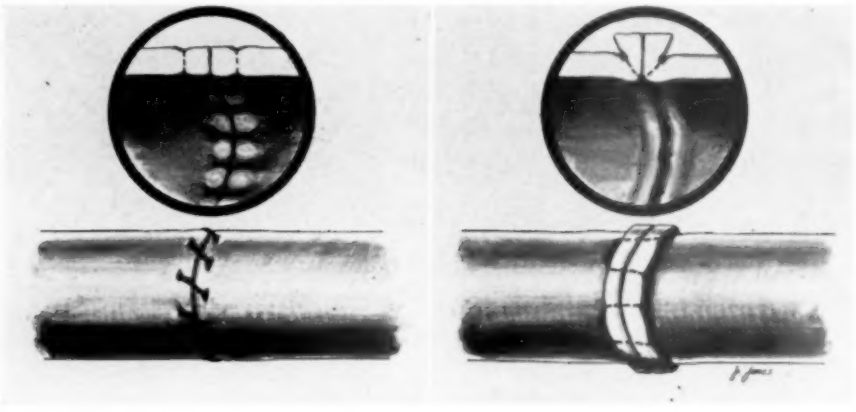
mattress and the end-on coaptation methods were employed on the right and left sides, respectively. The ends to be joined were biangulated with stay sutures and then united with a continuous suture.

Vein-Vein Anastomoses.—In a second group of twenty-five dogs under Nembutal anesthesia, 100 anastomoses were performed. In each dog, both external jugular veins and both femoral veins were divided and then repaired. The everting mattress and end-on coaptation methods were employed on the right and left sides, respectively. The ends to be joined were either biangulated or triangulated and then united with a continuous suture.



A. *B.*

Fig. 1.—Diagram illustrating two vascular anastomoses, one (*A*) performed by the continuous end-on coaptation suture method and the other (*B*) performed by the continuous everting mattress suture method. Which is the preferable method to use for an artery-artery, a vein-vein, or an artery-vein-artery anastomosis? In the experiments on paired vessels reported in this paper, the continuous end-on coaptation suture method was used on the left vessel, while the continuous everting mattress suture method was used on the right vessel.

Artery-Vein-Artery Anastomoses.—In a third group of twenty-one dogs, forty-two fresh autogenous vein grafts were implanted into the femoral artery. On each side, a segment of the femoral vein was resected, reversed, and then used to bridge a defect in the femoral artery. On the left side, the end-on coaptation technique method was employed for both anastomoses in all dogs. On the right, the everting mattress method was employed for both anastomoses in ten dogs, while in the remaining eleven dogs, the everting mattress method was used for the upper anastomosis, and the end-on coaptation method was used for the lower anastomosis. As in the vein-vein anastomoses, the ends to be joined were either biangulated or triangulated and then united with a continuous suture.

RESULTS

The incidences of thrombotic occlusion of anastomoses in these three series at the end of a six weeks' postoperative period are listed in Tables I, II, and III. It is to be emphasized that the results are comparisons of the continuous everting mattress method on the right side with the continuous end-on coaptation method on the left side in the same animal and carried out by the same operator. There were no significant differences in the results obtained by the

two of us. At the time of excision, the patent vessels had well-healed suture lines without stenosis, except in seven vessels. In one of these, stenosis was clearly the result of catching the opposite wall with a stitch at the time of the operation. In the other six vessels, the cause of the stenosis was not apparent.

TABLE I. INCIDENCE OF THROMBOTIC OCCLUSION OF CANINE ARTERY-ARTERY ANASTOMOSES, PERFORMED IN PAIRED ARTERIES BY THE CONTINUOUS EVERTING MATTRESS METHOD ON THE RIGHT SIDE AND BY THE CONTINUOUS END-ON COAPTATION METHOD ON THE LEFT SIDE (TABULATIONS ARE ON THE BASIS OF RESULTS OBTAINED WITHIN INDIVIDUAL ANIMALS)

CAROTID ANASTOMOSES			FEMORAL ANASTOMOSES	
NO. OF DOGS	% TOTAL	RESULT	NO. OF DOGS	% TOTAL
21	84	Both sides open	17	68
1	4	Both sides closed	2	8
3	12	Everting open and end-on closed	3	12
0	0	Everting closed and end-on open	3	12
25	100	Totals	25	100

TABLE II. INCIDENCE OF THROMBOTIC OCCLUSION OF CANINE VEIN-VEIN ANATOMOSES, PERFORMED IN PAIRED VEINS BY THE CONTINUOUS EVERTING MATTRESS METHOD ON THE RIGHT SIDE AND BY THE CONTINUOUS END-ON COAPTATION METHOD ON THE LEFT SIDE (TABULATIONS ARE ON THE BASIS OF RESULTS OBTAINED WITHIN INDIVIDUAL ANIMALS)

EXTERNAL JUGULAR ANASTOMOSES			FEMORAL ANASTOMOSES	
NO. OF DOGS	% TOTAL	RESULT	NO. OF DOGS	% TOTAL
24	96	Both sides open	19	76
0	0	Both sides closed	1	4
0	0	Everting open and end-on closed	3	12
1	4	Everting closed and end-on open	2	8
25	100	Totals	25	100

TABLE III. INCIDENCE OF THROMBOTIC OCCLUSION OF FRESH AUTOGENOUS CANINE VEINS IMPLANTED BILATERALLY INTO THE FEMORAL ARTERY (TABULATIONS ARE ON THE BASIS OF RESULTS OBTAINED WITHIN INDIVIDUAL ANIMALS)

RIGHT SIDE, UPPER ANASTOMOSIS BY CONTINUOUS EVERTING MATTRESS METHOD AND LOWER ANASTOMOSIS BY CONTINUOUS END-ON COAPTATION METHOD, WHILE ON LEFT SIDE, BOTH ANASTOMOSES BY CONTINUOUS END-ON COAPTATION METHOD			RIGHT SIDE, BOTH ANASTOMOSES BY CONTINUOUS EVERTING MATTRESS METHOD, WHILE ON LEFT SIDE, BOTH ANASTOMOSES BY CONTINUOUS END-ON COAPTATION METHOD	
NO. OF DOGS	% TOTAL	RESULT	NO. OF DOGS	% TOTAL
1	9	Both sides open	4	40
3	27	Both sides closed	4	40
3	27	Right side open and left side closed	0	0
4	37	Right side closed and left side open	2	20
11	100	Totals	10	100

In many instances of artery-artery and of vein-vein anastomoses, a moderate degree of narrowing was present at time of operation in those anastomoses performed by the continuous everting mattress method in which a generous cuff was turned out. At the time of excision six weeks later, the cuff was no longer visible, and the narrowing present at operation had disappeared in most instances.

In the artery-artery anastomoses, the average outside diameters, at operation, of the carotid and femoral artery anastomoses that remained patent were 3.65 mm. and 3.37 mm., respectively. Of those that later closed, the average outside diameters were 3.85 mm. and 3.19 mm., respectively. In the vein-vein anastomoses, the average outside diameters, at operation, of the external jugular and femoral vein anastomoses that remained patent were 5.81 mm. and 4.25 mm., respectively. Of those that later closed, the average outside diameters were 5.0 mm. and 3.88 mm., respectively. In the vein-vein anastomoses, the incidence of thrombosis was not related to whether the ends to be joined were biangulated or triangulated. In the artery-vein-artery group, however, the results were better with triangulation than with biangulation. These observations do not prove whether or not triangulation is superior to biangulation. In this latter group, at operation, the average outside diameter of the artery 1 cm. above the upper anastomosis in those grafts that remained patent was 3.03 mm., while it was 3.01 mm. in those that became occluded.

DISCUSSION

The results are summarized in graphic form in Fig. 2. In both the artery-artery and vein-vein series, high percentages of the anastomoses made by either suture method remained patent. Observed differences in thrombotic occlusion were not significant. Although larger percentage differences were observed in the artery-vein-artery anastomoses, their statistical significance is questionable on the basis of small numbers. The most surprising fact derived from these studies is that small-caliber veins of the dog can be repaired with a high degree of success by either suture method. In no instance was a trailing thrombus found attached to the suture line, and no clinical evidence of pulmonary embolism was observed in any dog. These data are probably transferable to the human patient. In the correction of arteriovenous fistulas at Walter Reed Army Hospital and in the surgical management of vascular injuries in Korea, the repair of major veins of the extremities has proved beneficial to the patient. Hughes* repaired major veins without clinical evidence of thrombotic occlusion or of pulmonary embolism in each of thirteen patients in Korea.

The data reported in this paper indicate that in the hands of both of us it is unimportant whether the everting mattress or the end-on coaptation method of vascular repair be employed. Of importance are vessel caliber and the diameter relationships of the vessels joined together. In a recent consecutive series of 443 anastomoses in the thoracic aorta of the young pig, in which autogenous, homogenous, and heterogenous arterial grafts and Orlon tubes

*Hughes, C. W., Division of Surgery, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.: Personal communication.

were implanted, anastomotic occlusion has not been observed in spite of frequent graft-aortic diameter disproportions. This does not imply exceptional technique. Rather, it indicates that where the volume of blood flow is large, thrombosis is rare even with diameter disproportion. Conversely, where volume flow is less and diameter disproportion is present at the anastomosis, the incidence of thrombosis is high. Such was the case in our series of artery-vein-artery anastomoses where the concomitant vein was used.

Triangulation of the ends to be joined in vein-vein and artery-vein-artery anastomoses may be an aid to accurate placement of stitches with avoidance of catching the opposite wall.

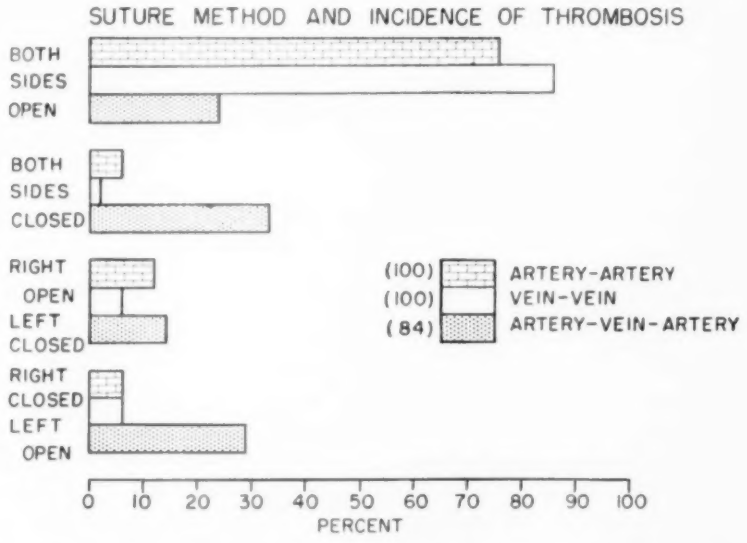


Fig. 2.—Graph summarizing the influence of the suture method upon the incidence of thrombosis in the 284 vascular anastomoses reported in this paper. A comparison is shown of the results obtained in repairing paired vessels within the same animal. The left vessel was repaired by the continuous end-on coaptation suture method in all instances. The right vessel was repaired by the continuous everting mattress suture method in all instances except eleven. These exceptions were the lower artery-vein-artery anastomoses, which were performed by the continuous end-on coaptation suture method. These results are not shown separately, but rather are grouped together with the ten instances on the right side in which both artery-vein-artery anastomoses were performed by the continuous everting mattress suture method. The parenthetic numbers in the key represent the total number of anastomoses in each group.

The dangers in vascular repair are different in large- and small-caliber vessels. In large-caliber arteries, as the thoracic aorta, thrombosis is rare following repair, but blood loss for the inexperienced operator may be extreme. The reverse is true for small-caliber arteries. Here, thrombosis is more frequent and blood loss less.

SUMMARY

The relation of the incidence of thrombosis to suture method in 284 anastomoses in a carefully controlled experimental study in dogs of artery-artery, vein-vein, and artery-vein-artery anastomoses has been presented.

In many instances of artery-artery and of vein-vein anastomoses, a moderate degree of narrowing was present at time of operation in those anastomoses performed by the continuous everting mattress method in which a generous cuff was turned out. At the time of excision six weeks later, the cuff was no longer visible, and the narrowing present at operation had disappeared in most instances.

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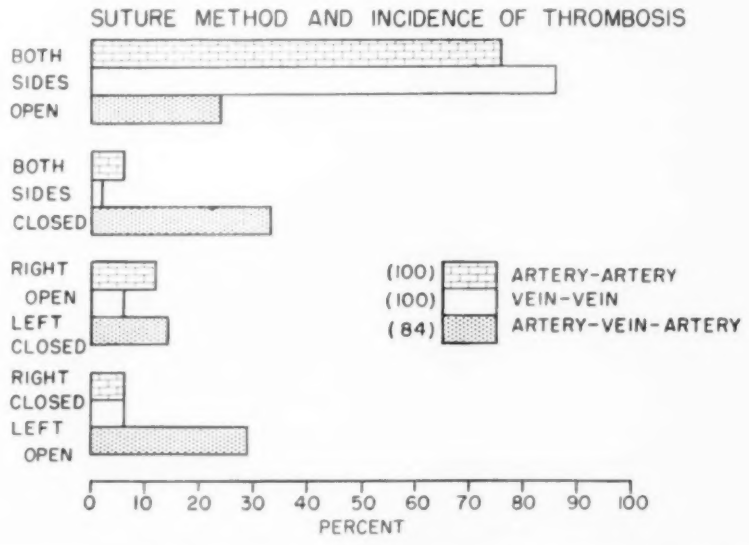

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SUMMARY

The relation of the incidence of thrombosis to suture method in 284 anastomoses in a carefully controlled experimental study in dogs of artery-artery, vein-vein, and artery-vein-artery anastomoses has been presented.

CONCLUSIONS

1. In our hands, the incidence of thrombotic occlusion in small-caliber canine artery-artery anastomoses is low and is independent of whether the continuous everting or end-on coaptation suture method be used for the repair.

2. In our hands, the incidence of thrombosis in repairs of small- and medium-caliber canine veins is low and is not influenced by whether the continuous everting or end-on coaptation suture method be used for the repair.

3. In our hands, it is doubtful if the incidence of thrombotic occlusion of small-caliber canine artery-vein-artery anastomoses is related to whether the continuous everting or end-on coaptation suture method be used for the repair.

DISTAL OPERATIVE ANGIOGRAPHY AS AN AID IN ENDARTERECTOMY

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TECHNICAL advances have improved the results of endarterectomy for occlusive atherosclerotic vascular disease. Accurate choice of good candidates for the operation remains a problem. After clinical identification of patients with isolated obstructions and with no serious gross arteriosclerotic manifestations elsewhere, preoperative angiography is used to identify the site and extent of the obstruction. Where the obstruction is short or relatively high (upper femoral or iliac), preoperative angiograms are usually satisfactory. Where the obstruction, however, is very long (greater than 25 cm.) or where the collateral is poorly developed or when the series of films misses the bolus of dye as it refills the distal segment, the surgeon needs further information before submitting the patient to the hazards of endarterectomy.

If no refilling of the distal segment is seen, the first problem is the demonstration of a patent and satisfactory artery above the level of the bifurcation of the popliteal artery. The second point to be ascertained is the patency of the system beyond such a demonstrably satisfactory popliteal segment. The presence of severe obliterating vascular disease in the vessels of the calf greatly reduces the chances of a successful endarterectomy.

METHOD

All otherwise satisfactory surgical candidates whose femoral arteriograms fail to show the distal segment clearly are subjected to low femoral or popliteal artery exploration. A longitudinal incision is begun in the lower thigh over the femoral artery and is extended across the popliteal space transversely if necessary. The popliteal space and artery are explored only if the distal femoral artery is not suitable. Exposure of the popliteal space is accomplished by dividing the common fibrous attachments of the semimembranosus, semitendinosus, and gracilis muscles, sparing the gastrocnemius. If a soft and patent vessel is found, an arteriogram is taken. Arteriography by the same technique is performed on those patients whose preoperative femoral angiograms have shown a presumably satisfactory distal vessel, in order to visualize the arterial tree in the calf.

A No. 20 gauge needle is inserted into the artery, and if blood can be drawn back, 10 c.c. of dilute heparin solution (10 mg. per 100 c.c.) is injected. The x-ray cassette is placed in a pillowcase beneath the knee and calf, and a

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portable x-ray unit is used for exposure. Ten or fifteen cubic centimeters of one of the organic iodine contrast media in aqueous solution (Diodrast, Neo-Iopax, or Urokon) is used as the contrast medium and is injected through this same needle. The arteriographic injection is followed by another dose of intra-arterial heparin.

If a thick-walled vessel is found or if it is not possible to get blood back by aspiration, the artery is opened longitudinally between tapes. A fine polyethylene catheter is passed distally into the cleft of a lumen if such can be demonstrated. A tape is temporarily tied about the catheter, and the injections are performed through it.

Fig. 1.—Distal operative angiogram showing patent popliteal and anterior tibial arteries. There is some disease in the posterior tibial artery (Case 1).

RESULTS

This technique has been applied to eleven patients since August, 1952. No deleterious effects have been observed. On six occasions it has been possible to proceed with successful endarterectomy in a patient not previously believed to be a good candidate. In only two of these six patients had any filling of the popliteal vessel been seen on the initial angiogram. In three patients, such extensive disease was found that in spite of apparently hopeful preoperative angiograms, no endarterectomy was attempted. These three patients had concomitant gangrene or necrosis, and early amputation was performed on the basis of the angiographic findings. Confirmation of the presence of a normal popliteal artery and demonstration of normal distal calf vessels were obtained in one patient. In the remaining patient, marked distal obstruction was found due to an organized intra-arterial thrombus, and the popliteal bifurcation itself was thickened. In spite of these ominous findings, endarterectomy over a distance of 46 cm. was performed because of the presence of gangrene in the toes and impending necrosis of the heel. Early thrombosis and failure occurred.

CASE REPORTS

The following case reports are illustrative.

CASE 1.—H. C. H., a 44-year-old white man, had a history of claudication in the left calf of nine months' duration. Preoperative angiogram demonstrated an obstruction in the proximal superficial femoral artery and failed to show any filling of the distal segment. Lumbar sympathectomy was performed without relief. As a last resort, exploration of the left popliteal artery was performed and revealed a satisfactory artery locally and a patent tree distally (Fig. 1). Endarterectomy was performed over a distance of 36 cm. Six months later the patient had no complaints of arterial insufficiency and had normal pedal pulsations.

CASE 2.—R. M., a 62-year-old Negro man, had a history of claudication of fourteen months' duration and on admission had impending necrosis of the foot and lower leg. Preoperative angiogram showed a faint filling of the popliteal artery (Fig. 2). The upper limit of the obstruction was in the mid-thigh. Exploration of the popliteal artery revealed a thick-walled but patent artery. Angiography at this time revealed extensive obstruction of the major arteries in the calf with only a few tortuous fine vessels by-passing the obstructions (Fig. 3). Endarterectomy was abandoned. Arteriectomy of the lower femoral artery was performed, but because of unabated pain and extending necrosis, low-thigh amputation was performed thirteen days later.

Fig. 2.—Preoperative angiogram showing faint refilling of the popliteal artery and its bifurcation (Case 2).

Fig. 3.—Distal operative angiogram showing previous (Fig. 2) popliteal segment and extensive arterial narrowing in the proximal anterior and posterior tibial arteries (Case 2).

CASE 3.—C. W., a 41-year-old white man, had a history of arterial insufficiency with intermittent claudication and ulceration of the toes and heel of the right leg of two months' duration. Lumbar sympathectomy gave slight subjective relief. Angiograms failed to show any refilling of the popliteal segment. The upper limit of the obstruction was in the mid-thigh. Exploration revealed a patent popliteal artery, but distal angiography demonstrated almost complete obstruction of the popliteal bifurcation and of the vessels in the calf. Because of the extensive pedal gangrene, an immediate low-thigh amputation was performed. It is believed that the rehabilitation of this patient was greatly aided by prompt identification of the severity of the disease and early amputation.

CASE 4.—J. J. M., a 50-year-old white diabetic man, had a three-week history of cellulitis of the right foot with wet gangrene of two toes. Arteriogram showed no clear-cut refilling of the distal segment. The upper limit of the obstruction was in the lower thigh. Exploration and open arteriogram showed extensive popliteal thickening and arterial obstructions in the distal calf. Endarterectomy was abandoned, but a polyethylene catheter was left in place in the artery. Immediate open amputation of the toes was performed. During the next forty-eight hours, penicillin and histamine were administered regionally through the catheter, and there was marked subsidence of the inflammatory reaction. On the sixth postoperative day, a thin split-thickness graft was placed over the amputation site. At first this appeared to be healing, but necrosis of the edges of the amputation site appeared and progressed. Below-knee amputation was successfully accomplished three weeks later.

CONCLUSIONS

Selection of patients for the formidable operation of endarterectomy remains a problem. Of particular interest have been those patients with either no refilling of the distal popliteal segment on angiography, or with questionably satisfactory distal vessels. The benefits of the operation may be extended to some of this group, and the hazards withheld from others on the basis of the technique of exploration and operative distal angiography which has been described.

PRODUCTION OF AORTIC INSUFFICIENCY WITH A STUDY OF ARTERIAL TRACINGS

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(From the Charles P. Bailey Thoracic Clinic, and Hahnemann Medical College and Hospital, with the support of the Mary Bailey Foundation for Heart and Great Vessel Research)

AORTIC valvular surgery plays an important role in experimental heart surgery, especially in attempts to correct aortic insufficiency. The first step of such an experiment is production of aortic insufficiency, and the second step is correction of this organic and hemodynamic defect. This article is concerned with the first stage of the experiment.

LITERATURE

This type of experimental work was performed by Smithy,[1] Litwak,[2] and Redondo-Ramirez.[3] Smithy in 1948 described a method of producing aortic regurgitation by using a hooked instrument which divided the aortic cusp by a transaortic approach. The disadvantage of this method is that it does not produce a lack of valvular substance and, therefore, is unlike the pathology of human rheumatic aortic insufficiency. Litwak described in 1952 a method of producing aortic insufficiency by removing the substance of the cusp with a special clamp by means of a transventricular approach. As this method of transventricular approach is time consuming, it is unsuitable for the production of aortic regurgitation in large numbers of animals. We have developed a simple, accurate method, using a backward cutting punch. Blood pressure tracings were recorded by using a two-channel Lilly manometer. A mercury manometer was used for control of mean pressure.

MATERIAL AND METHODS

Twenty-one dogs weighing from 15 to 55 pounds were used. The instrument is a backward cutting punch† (Fig. 1). It is formed of two parts: a cutting mouth-tip, and a universal handle which is able to remove a part of the aortic cusps, about ⅔ square centimeter, as shown in the illustration. For arterial tracing, we have used the Lilly manometer and mercury manometer simultaneously.

Pentobarbital sodium was used, 50 mg. per 5 pounds of weight, given intravenously, with endotracheal intubation. The respiration was controlled by a positive pressure respirator‡ with a pressure of 15 to 25 mm. Hg.

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†Made by George P. Pilling & Son Company, Philadelphia, Pennsylvania.

‡Pneophore made by Mine Safety Appliance Company, Pittsburgh, Pennsylvania.

The left side of the chest was shaved, and the animal was placed on the table in the left lateral position. The neck and groin were prepared for arterial cannulation. Skin preparation was carried out with pHisoderm and Tincture of Merthiolate.

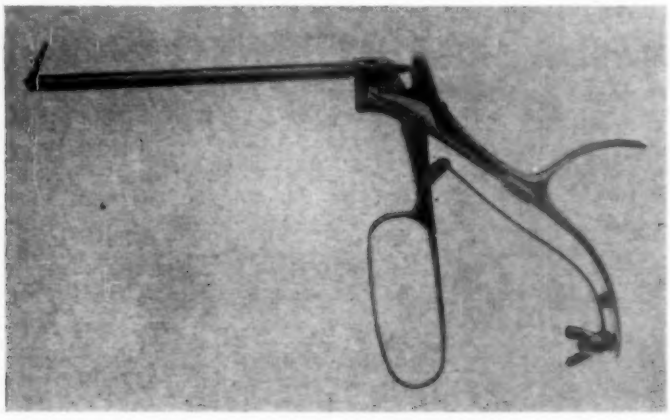


Fig. 1.—Instrument used for producing aortic insufficiency.

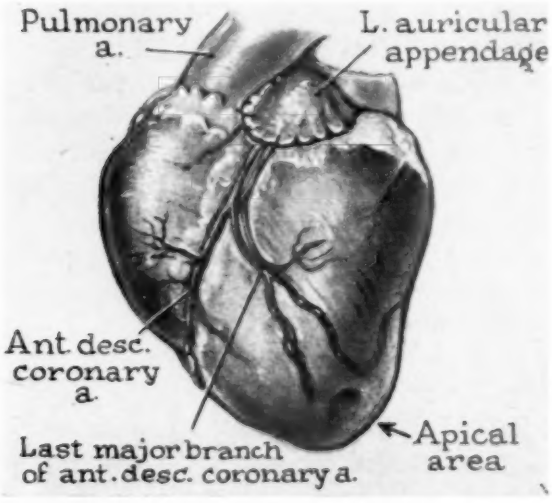


Fig. 2.—Anterolateral aspect of dog's heart showing anterior descending branch of left coronary artery.

Operation.—The chest was opened through the fifth intercostal space. One 10 c.c. ampule of procaine was injected into the pericardial sac. A purse-string suture was applied in the left ventricle close to the apex in an area similar to that used to insert the aortic dilator in performing aortic commissurotomy in human beings. It is important to be aware of the following facts:

1. As is shown in Fig. 2, the safe entrance of the instrument into the left ventricle is a limited area close to the apex of the heart, between the anterior descending branch of the left coronary artery and its last branch on the surface of the left ventricle. There is no danger of injuring the papillary muscle or chordae tendineae at this area.

2. The weakest portion of the left ventricle is at the apex, and it is not suitable for instrumentation.

3. We have divided the surface of the left ventricle into three zones, as shown in Fig. 2: apical, preapical or safe zone, and dangerous zone—the remainder.

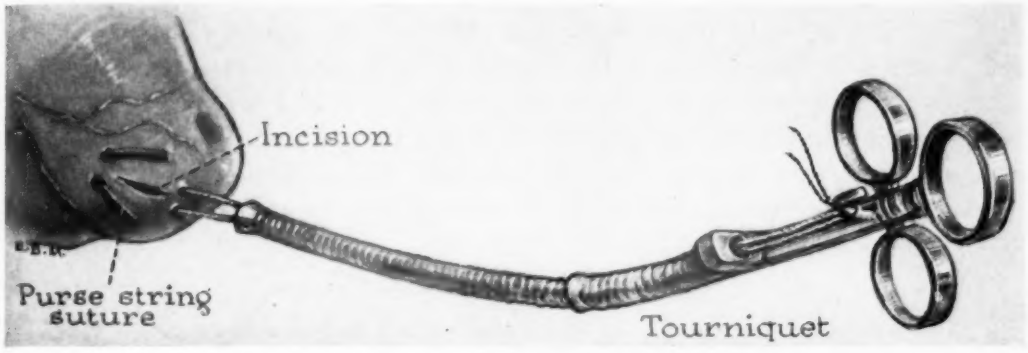


Fig. 3.—Rumel tourniquet attached to purse-string suture in periapical zone of left ventricle of dog's heart.

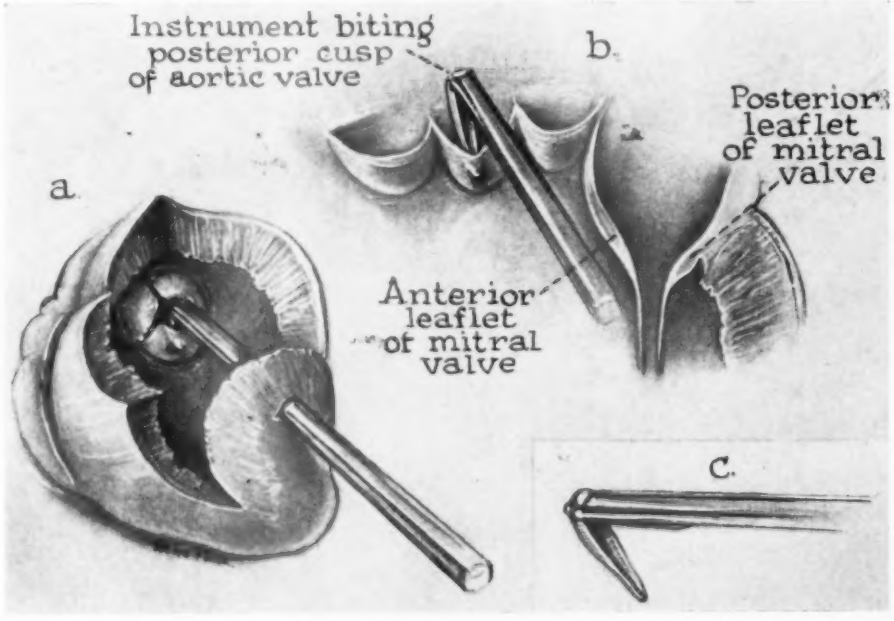


Fig. 4.—Instrument in place in aorta with tips open and ready to remove portion of posterior cusp.

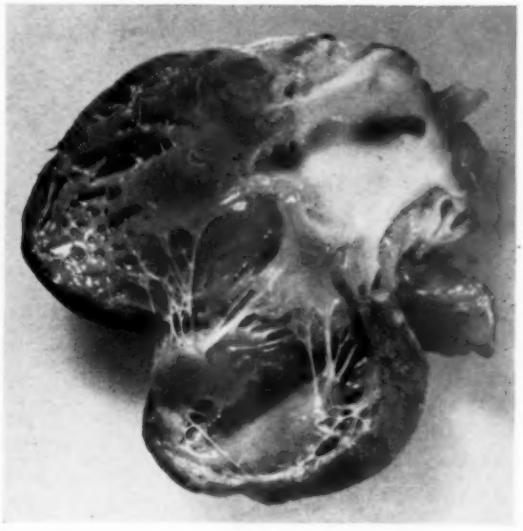
4. In performing aortic commissurotomy in human cases, we have seen ventricular fibrillation due to splitting of the papillary muscle at the time of entering the ventricle through the dangerous zone (especially the right upper part of the surface of the right ventricle).

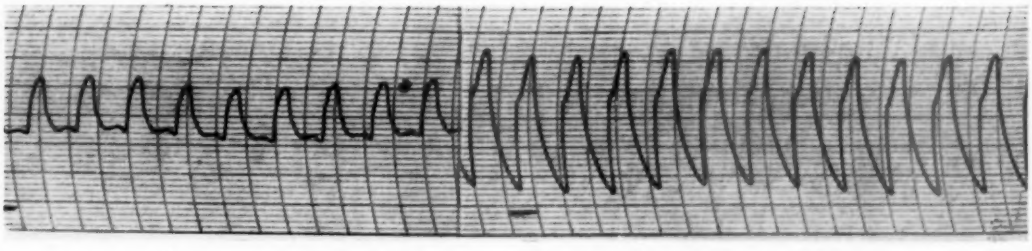
To control the purse-string suture on the ventricle, we used a Rumel tourniquet* (Fig. 3). The stab wound was made in the myocardium, and the punch was introduced into the aorta from the ventricular cavity. The handle of the punch should be in the upward position and the mouth-tip closed. The

*Manufactured by George P. Pilling & Son Company, Philadelphia, Pennsylvania.

left index finger should serve as a guide from the outside for introducing the instrument into the aorta. After the tip is in the descending aorta, the mouth of the punch is opened thirty to forty-five degrees (Fig. 4). The instrument should be pulled out slowly and gently until the resistance of the posterior valvular cusp which is caught in the mouth of the instrument is felt. At this time the punch is closed, and then pulled out. The incision in the ventricle is closed with a few interrupted No. 000 cotton sutures. The diastolic murmur due to the regurgitation is 3 plus to 4 plus. We leave the pericardium open, and we close the chest by interrupted chromic or cotton pericostal sutures; we use cotton for muscle, and wire for skin. We have used procaine penicillin (600,000 units at the time of surgery, and also 600,000 units the next day).

A.





B.

Fig. 5.—Heart (*A*) and postoperative tracing (*B*) of Dog No. 1024, showing defect in posterior cusp and abolishment of dicrotic notch.

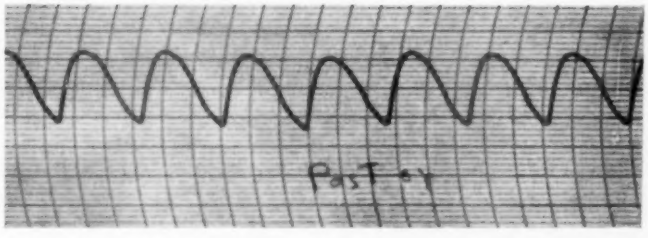
Tracings obtained from the carotid or femoral artery show higher systolic and lower diastolic pressures with wide variations in pulse pressure. The tracings also show a straighter anacrotic limb and abolishment of the

already low dicrotic notch which was present in the preoperative and postoperative tracings. The variations of pressure in our last five dogs were as follows:

Preoperatively	*Postoperatively*
140/90	160/40
78/45	120/40
120/80	125/70
130/90	140/48
120/75	145/40

The variations in the blood pressure are roughly related to the amount of cusp tissue which was removed. The diastolic pressures are more nearly uniform than the systolic. To check the pressure change in the Lilly manometer, we have added a mercury manometer by using an extra-arterial

A.



B.

Fig. 6.—Heart (*A*) and postoperative tracing (*B*) of Dog No. 801 and defect in posterior cusp.

cannulation. There is usually a difference of 10 mm. between the mean pressure as measured by the mercury manometer and that measured by the Lilly manometer when the special mean pressure switch is turned on. As shown

in Fig. 5, in Dog No. 1024, the amount of the defect in the posterior cusp was less than one-third of the whole cusp; the tracing shows a low dicrotic notch preoperatively which is abolished in the postoperative tracing, and also the change of pulse pressure is well demonstrated. In Dog No. 1045, there was a hole in the posterior cusp which was made by our instrument in the manner described previously. The postoperative tracing revealed a straight anacrotic and dicrotic limb. In Dog No. 1044, the defect was about one-fourth the whole posterior cusp, and abolishment of the dicrotic notch with wide pulse pressure was demonstrated. In Dog No. 709, the preoperative and postoperative range of manometer readings was different, and so the change of pulse pressure was not well demonstrated in the tracing, but the change in the shape of the tracing with abolishment of the dicrotic notch was clear; also the hypertrophic left ventricle was shown in the tracing. In Dog No. 801, as shown in Fig. 6, the defect is shown with the abolishment of the dicrotic notch postoperatively. In the remainder of the dogs, the results closely resembled results in these five cases.

Of twenty-one dogs, five were used for developing the technique, and two of these dogs died, one when the instrument punctured the aorta, and the other because of removing most of the posterior cusp. We have found that a defect of more than one-third of the cusp is intolerable for the left ventricle even with preoperative digitalization. The mortality in the last sixteen dogs was 12 per cent. The cause of this was ventricular fibrillation and cardiac arrest. This can be diminished appreciably by limiting the size of the defect to not more than one-third of the whole cusp, by injecting procaine into the myocardium in the operative zone, and by assisting cardiac contraction by massage immediately after the production of regurgitation. We found hypertrophy of the left ventricle in all dogs at the time they were sacrificed.

SUMMARY

A technique for producing aortic insufficiency similar to the rheumatic aortic insufficiency found in human beings is described. Twenty-one dogs were used with very good results. Arterial tracing studies have shown a significant change according to the degree of insufficiency. Left ventricular hypertrophy was noted after two weeks postoperatively.

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THE METABOLISM OF FRUCTOSE IN MAN

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INTRODUCTION

IT HAS recently been suggested that solutions containing fructose have certain advantages in the parenteral alimentation of patients. Interest in this subject has led to a number of reports relating to the utilization of fructose in man. There has been particular reference to comparison between the effect of administration of fructose with that of glucose. A comprehensive review of the metabolism of fructose was presented in 1936 by Deuel.[13] The greater part of the investigations up to that time had dealt with studies in experimental animals, and more recently numerous observations have been made on patients. An analysis of the recent studies seemed indicated in an effort to assess better the present status of fructose in parenteral fluid therapy. This review is concerned primarily with the findings in patients with normal carbohydrate metabolism and with the changes in metabolism encountered after operative procedures.

Effect of Intravenous Infusion of Fructose on Blood Sugar Levels.—It has been demonstrated that the intravenous injection of fructose in both man and in experimental animals is followed by rapid disappearance of the substance from the blood. There is general agreement that the intravenous administration of fructose results in elevation of total blood sugar that is less pronounced than that associated with the injection of similar quantities of dextrose. In our laboratory, fasting blood fructose levels ranged from 2 to 6.9 mg. per 100 ml. With the injection of 10 per cent fructose at rates of 0.40 to 0.45 Gm. per kilogram per hour, a maximum increase to 89.6 mg. per 100 ml. was encountered. Miller and associates[19] reported an average rise to 81 mg. per 100 ml. with an injection rate of 1 Gm. of fructose per kilogram per hour.

An accompanying elevation in the blood glucose level was detected in our previous experiments.[2] This finding has been confirmed by further studies (Fig. 1). This is somewhat at variance with the experimental studies of Bollman and Mann[6] and that of Wierzuchowski,[30] who did not demonstrate significant changes in the blood glucose of dogs receiving fructose intravenously. Corley[12] also stated that the presence of fructose did not always produce a rise in blood glucose. However, more recently Miller[19] noted a rise in the blood glucose level

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in two of three patients with normal carbohydrate metabolism when fructose was injected. While performing fructose tolerance tests, Smith and his associates[25] found a mean rise in blood glucose of 4.0 mg. per 100 ml. thirty minutes

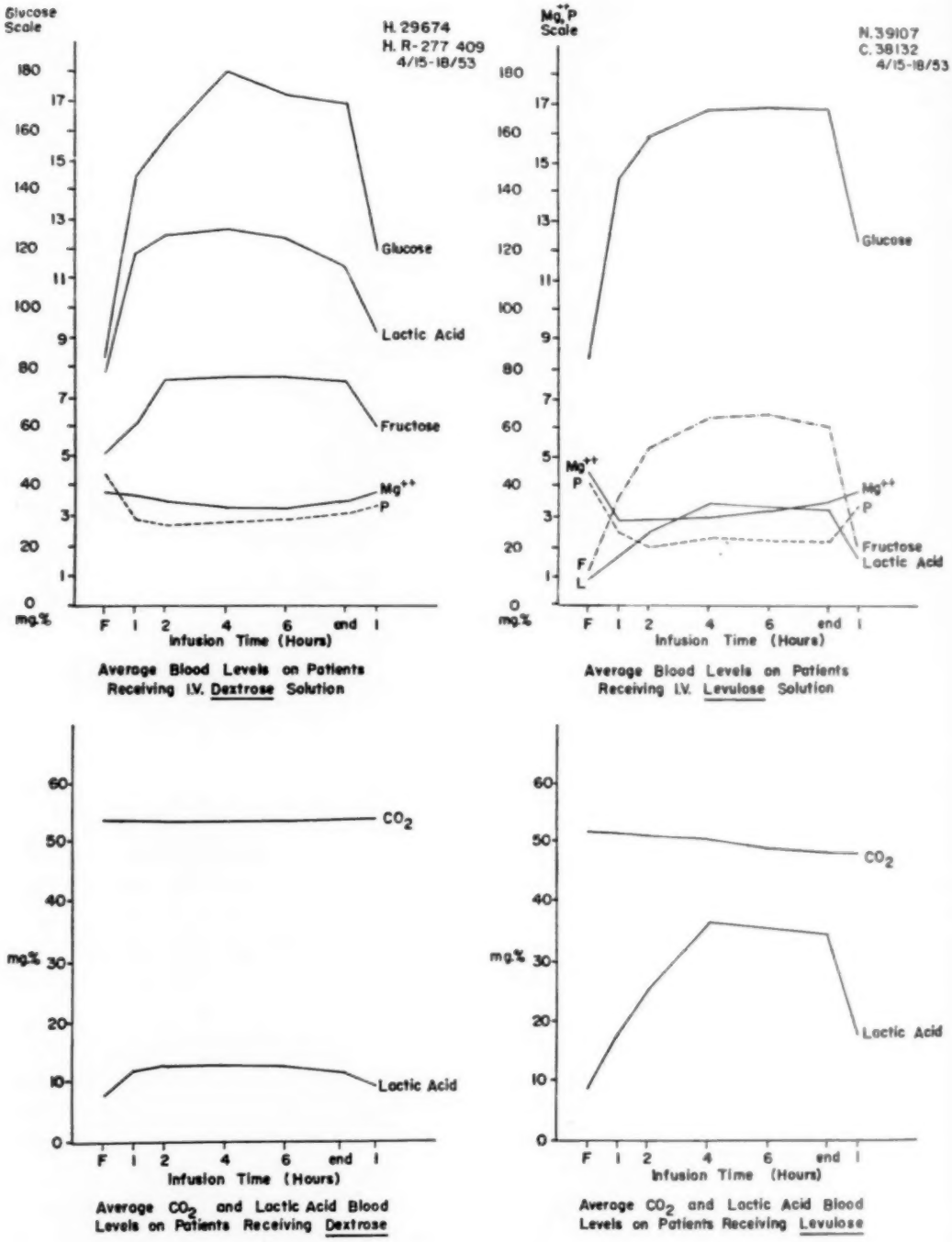

Fig. 1.—Chart showing average blood levels following the infusion of 200 Gm. of fructose or glucose at average rates of 0.33 to 0.45 Gm. per kilogram per hour in patients with normal carbohydrate metabolism. The determininations were made on each of four patients daily for four consecutive days.

following the administration of 0.5 Gm. of fructose per kilogram over a thirty-minute period.

Thus, it appears that in man the intravenous administration of fructose results in increases in both the blood fructose and blood glucose levels. In general, it has been noted that the increase of each of these blood levels is somewhat less pronounced than the rise in blood glucose following the injection of comparable quantities of glucose. However, our recent studies indicate that the total blood sugar response may, in some individuals with normal carbohydrate metabolism, be the same (Fig. 1).

Effect of Fructose on Blood Lactic Acid and Pyruvic Acid Levels.—Himwich[16] has stated that the administration of fructose causes an accumulation of lactic acid which is exceeded only by the administration of dioxyacetone. It is well established that a rise in the blood pyruvic acid level follows the injection of fructose.[13, 19, 23, 25] The blood levels of both acids are higher than those observed after the administration of glucose.[19, 23] It is also known that these changes in the blood levels of lactic acid and pyruvic acid occur in the diabetic individual as well as in the normal person following the injection of fructose.[19, 25]

In a group of eight experiments on patients with normal carbohydrate metabolism, we found that the blood lactic acid level rose from an average fasting level of 8.8 mg. per 100 ml. to 10.8 mg. per 100 ml. following the administration of 10 per cent glucose. In a similar series with 10 per cent fructose, the blood lactic acid level rose from an average fasting level of 8.3 to an average maximum of 38.4 mg. per 100 ml. This marked rise in the blood lactic acid level was associated with a diminished CO_2 combining power of the blood in each case (Fig. 1). This has received comment by both Himwich[16] and by Root and associates.[23] In each instance in our studies, CO_2 combining power returned toward normal with the completion of the infusion of fructose and as the lactic acid levels of the blood fell to normal ranges.

In addition to the changes described, Smith[25] found marked elevation of alpha-ketoglutaric acid levels in both normal and diabetic individuals after fructose infusions.

Effect of Administration of Fructose on Blood Electrolytes.—A decrease of the serum inorganic phosphorus level follows the administration of fructose, which is more marked than that associated with the injection of glucose. Wierzuchowski[30] noted a maximum decrease three hours after the initiation of the fructose injection in dogs. Smith[25] has indicated that the fall in the serum inorganic phosphorus level is more rapid with fructose infusion and more prolonged with the injection of glucose. Miller and associates[19] have confirmed the observations of Root[23] that the depression of the serum inorganic phosphorus levels following the administration of fructose is similar in diabetic persons, in contrast to the lack of response to glucose in such individuals.

In our studies on patients with normal carbohydrate metabolism, the decrease in the level of serum inorganic phosphorus averaged 2.7 mg. per 100 ml. below the fasting level in the group receiving fructose with a range of from 1.5 to 3.2 mg. per 100 ml. In the group receiving similar quantities of glucose

(200 Gm.), the decrease in serum inorganic phosphorus ranged from 0.9 to 2.5 with an average fall of 1.5 mg. per 100 ml. These studies also appear to confirm the observations of Smith and associates[25] that the return to normal was prompt after fructose infusions and somewhat slower after the injection of glucose.

The pattern of change in the blood magnesium resembles that found with the serum inorganic phosphorus (Fig. 1). After the start of fructose infusions, a prompt fall in the magnesium level was noted which was greater and more abrupt than after glucose injections.

No significant alterations in the serum levels of sodium, potassium, or chloride were noted in our studies.

Urinary Excretion of Reducing Sugars Following Fructose Infusion.—In 1915, Woodyatt, Sansum, and Wilder[31] found that the tolerance limit for fructose, in prolonged and accurately timed injections, was approximately 0.15 Gm. per kilogram per hour or approximately one-sixth that of glucose. This appeared to be true for man, dog, and rabbit. Cori and Cori[10] found that fasting rats had a tolerance for fructose of 0.35 Gm. per kilogram per hour while in nonfasting rats a tolerance limit of 0.65 Gm. per kilogram per hour was determined. This was in contrast to 2.5 Gm. per kilogram per hour for glucose in nonfasting rats. These same workers also observed that when glucose or fructose was infused above the tolerance rate there was no marked difference in the rate of utilization of the two sugars.

It is recognized that fructosuria occurs even though the blood levels are low. Miller[19] found significant quantities of fructose in the urine even though the blood fructose level was as low as 4 mg. per 100 ml.

Certain discrepancies have been noted in various reports concerning the degree of mellituria resulting from the infusion of fructose in human beings. Most studies that have recently appeared have been based on observations made over a two- or three-hour period following the completion of the infusion. In normal subjects, Miller and associates[19] found that when 10 per cent fructose solution is given at a rate of 1 Gm. per kilogram, 5.1 to 7.4 per cent appeared in the urine within 120 minutes after the infusion ended. Weichselbaum and co-workers[29] gave 1 L. infusions of 10 per cent fructose to assorted patients at varying rates and found from 1.0 to 5.8 per cent of the fructose in the urine during the same length of postinfusion observation. Beal, Smith, and Frost[2] have found that the excretion of fructose in the urine continues beyond this period and that significant quantities of fructose may appear in four to six hours after the infusion has been completed. This last group, in studying patients with normal carbohydrate metabolism, found an average quantity of total reducing substances in the urine representing 6.6 per cent of the administered fructose when given in 1 L. quantities in 10 per cent concentration. When given daily for four to five days in 3 L. quantities each twenty-four hours, an average of 8.7 per cent appeared in the urine.

There have been some discrepancies in the published reports in comparing the relative quantities of glucose and fructose excreted when injected at comparable rates and concentrations. Miller and associates[19] have reported that

when similar quantities of fructose and glucose are administered to normal subjects, similar quantities appear in the urine. In contrast, Weichselbaum[29] found greater quantities of glucose than fructose in the urine under similar circumstances. Beal, Smith, and Frost[2] reported that the retention of glucose was better than that of fructose under comparable circumstances. This last report has been supported by similar findings by Smythe[26] and by Strub and associates.[28]

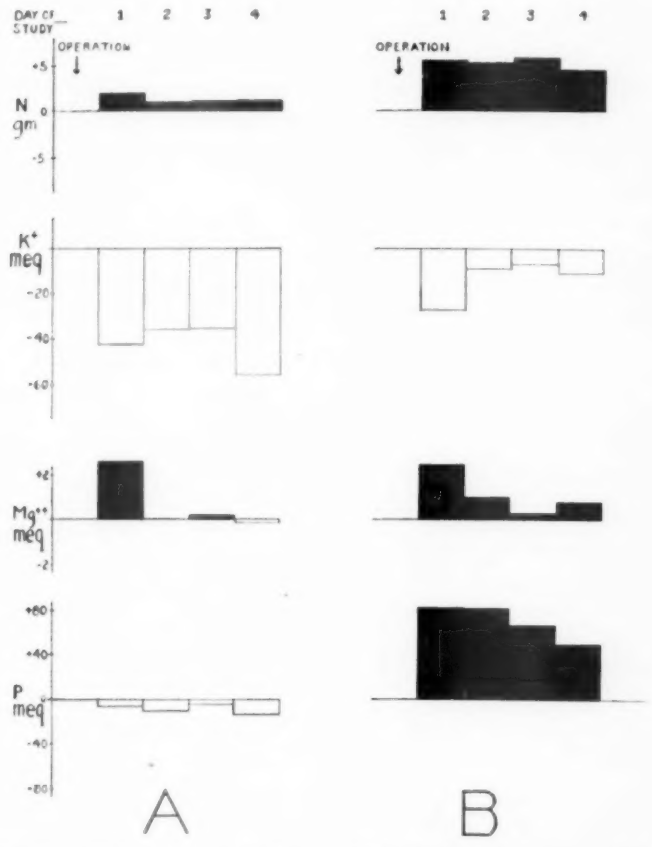

Fig. 2.—Balances studies on two patients. The solid black area above the zero line indicates positive balance and the open area below represents negative balance. Patient A received fructose (W. N., Table I) and Patient B received glucose (A. H., Table I).

Thus, at the present time, it appears doubtful that mellituria is diminished by the administration of fructose in contrast to glucose. Because it appears likely that significant quantities of fructose may appear in the urine several hours after completion of fructose infusions, further studies with repeated injections over longer periods of time should be carried out to answer this question better.

Influence of Fructose on the Urinary Excretion of Electrolytes.—Woodyatt, Sansum, and Wilder[31] found that the administration of glucose at rates below the tolerance limit of 0.8 to 0.9 Gm. per kilogram per hour in man did not result in an effect that could be interpreted as diuresis. On the other hand, they felt that the infusion of fructose at rates greater than 0.15 Gm. per

TABLE IA. TABULATION OF TWENTY-FOUR HOUR URINARY EXCRETION STUDIES OF PATIENTS RECEIVING INTRAVENOUS INFUSIONS OF 200 GM. FRUCTOSE OR GLUCOSE FOR FOUR DAYS FOLLOWING SUBTOTAL GASTRECTOMY FOR DUODENAL ULCER

PATIENT	DAY OF STUDY	URINARY VOLUME	Na^+ (MEQ.)	K^+ (MEQ.)	Cl^- (MEQ.)	N_2 (GM.)	P (MEQ.)	LACTIC ACID (MG.)	GLUCOSE (GM.)	FRUCTOSE (GM.)	Mg^{++} (MEQ.)
J. C., M. 37, 66.4 kg.	1	1,100	180	78.0	120.0	15.2	88.0	218.6	9.7	10.1	1.66
	2	3,240	190	97.0	101.0	15.0	93.0	367.1	9.8	10.2	2.5
	3	2,750	160	90.0	97.0	14.0	113.0	588.0	9.0	9.0	2.68
	4	2,340	159	83.0	67.0	14.2	107.0	674.0	9.3	9.7	2.18
W. N., M. 33, 59.1 kg.	1	2,000	171	83.0	96.0	14.0	111.0	360.0	11.8	10.96	1.4
	2	2,965	163	76.1	58.4	15.0	107.0	578.0	12.0	12.0	4.0
	3	1,840	179	76.0	67.4	14.9	113.0	751.0	12.8	11.5	3.8
	4	2,245	178	96.0	130.0	14.8	104.0	758.0	12.1	11.2	4.1
A. H., M. 44, 68.3 kg.	1	2,120	151	67.0	78.0	10.4	35.2	16.7	12.1	4.0	1.48
	2	1,810	142	49.3	104.0	10.6	35.9	26.8	9.67	14.0	2.9
	3	1,740	151	47.2	97.0	10.1	51.0	27.4	10.8	9.0	3.69
	4	1,842	154	51.4	103.0	11.3	68.1	16.7	9.6	17.0	3.15
W. H., M. 59, 79.6 kg.	1	1,765	96	38.0	67.0	9.0	23.4	56.0	8.8	9.0	1.42
	2	1,550	127	43.0	79.0	9.3	34.1	57.0	9.1	8.0	2.7
	3	1,670	130	54.0	68.0	9.8	35.3	29.0	10.3	17.0	2.26
	4	2,000	128	43.0	96.0	10.4	33.0	52.0	9.3	19.0	4.18

TABLE IB. DAILY INTRAVENOUS FLUID COMPOSITION BEGINNING DAY AFTER OPERATION

PATIENT	DAYS STUDIED	6% PROTEIN* HYDROLYSATE WITH 5% HEXOSE	10% HEXOSE (C.C.)	N (GM.)	HEXOSE (GM.)	K^+ (MEQ.)	Na^+ (MEQ.)	P (MEQ.)	Cl^- (MEQ.)	Mg^{++} (MEQ.)	AVERAGE INFUSION RATE (GM./KG./HR.)
J. C., M. 37, 66.4 kg.	4	2,000†	1,000†	16	200	40	155	118	155	4	0.45
W. N., M. 33, 59.1 kg.	4	2,000†	1,000†	16	200	40	155	118	155	4	0.40
A. H., M. 44, 68.3 kg.	4	2,000‡	1,000‡	16	200	40	155	118	155	4	0.37
W. H., M. 59, 79.6 kg.	4	2,000‡	1,000‡	16	200	40	155	118	155	4	0.33

*Protein hydrolysate used in these studies was 6 per cent Hyprotigen supplied by Don Baxter, Inc., Glendale, Calif.
†Solution containing fructose.
‡Solution containing glucose.

kilogram per hour resulted in diuresis. Hodgson, Iob, and Coon[17] found that the infusion of 10 per cent invert sugar resulted in a greater loss of sodium, chloride, and phosphorus than did similar quantities of glucose. These observations have recently been confirmed by Beal, Smith, and Frost,[2] who found a greater loss of sodium and potassium in the urine of patients receiving single 1 L. infusions of invert sugar or fructose as well as repeated 3 L. injections of fructose daily for four or five days. In the group receiving 1 L. infusions, the loss of potassium in the urine was approximately one and one-half times as great in the group receiving fructose and the loss of sodium barely three times. In Fig. 2, it may be seen the loss of potassium in the postoperative period was also markedly increased in a patient receiving fructose.

The administration of fructose has also been associated with an increased urinary excretion of phosphorus. In two patients who received 200 Gm. of fructose daily for four days following operation, the excretion of phosphorus averaged 5.8 Gm. as compared with an average of 3.02 Gm. of urinary phosphorus in two patients receiving equal quantities of glucose under similar conditions. A comparison of the balance resulting from this loss is illustrated in Fig. 2. The results are tabulated in Table I. Methods have been published elsewhere.[2, 4]

Magnesium excretion was also studied in these two patients, and it was felt that there was no significant difference in the two groups of studies.

Influence of the Administration of Fructose on Nitrogen Metabolism.—Fewer reports have dealt with this aspect of the metabolism of fructose than with its actual utilization.

Earlier reports by Bollman and Mann,[6] based on experiments on dogs, suggested that fructose administration resulted in a decreased urinary loss of nitrogen. This was interpreted as indication of a protein-sparing action. Albanese and associates[1] reported a greater protein-sparing action with fructose than with glucose administration, but oral route of administration was chiefly employed in these studies. In comparing the utilization of fructose with glucose, Elman[15] found that the use of fructose was followed by a variable but better nitrogen balance than was observed after either glucose or invert sugar. On the other hand, it was noted in these experiments that the loss of nitrogen was less in the group receiving glucose than in those receiving invert sugar. This latter finding has been supported by the experiments of Hodgson, Iob, and Coon,[17] who also found that nitrogen excretion was greater in patients receiving invert sugar when compared to similar experiments with glucose.

In our laboratory, each of four patients was given 1 L. of 10 per cent hexose sugar and 2 L. of 6 per cent protein hydrolysate containing 5 per cent hexose sugar daily.* The hexose in two patients was glucose and in the other two fructose. The patients were studied for four days and received no oral fluid or food during the period of observation.

In both instances the excretion of nitrogen was greater in the patients receiving fructose (Fig. 2). The patients to whom fructose was administered

*All intravenous solutions used in these studies were supplied through the courtesy of Don Baxter, Inc. The protein hydrolysate used was 6 per cent Hyprotigen.

were found to have from 14.0 to 15.2 Gm. of urinary nitrogen in each twenty-four hour urine collection as compared to 9.1 to 11.8 Gm. in the patients to whom glucose was administered.

Thus, there would appear to be some discrepancy in the reported findings; further and more prolonged studies would be of value in determining the possible anabolic influence of fructose.

Utilization of Fructose in the Period Following Operation.—Present evidence indicates that the metabolism of glucose is impaired in the period following operation but that the utilization of fructose remains unaltered.[14] In this regard, the response to the administration of fructose resembles that found in diabetes mellitus.[25] However, there seem to be some alterations in the utilization of fructose in the patient with diabetes and presumably in patients in the period following operation. Bollman and Mann[6] studied the utilization of fructose in pancreatectomized dogs and felt that there was better utilization of fructose than glucose. However, the superior effect gradually diminished and the amount of glucose in the urine increased. Joslin[18] also noted the loss of effectiveness in diabetic persons when fructose was given continuously. More recently, Miller[19] studied the effects of administration of fructose to diabetic persons. In these studies it was demonstrated that the diabetic person utilizes fructose to a greater extent than glucose. However, it was noted that there was a marked rise in the blood glucose level and in the urinary glucose excretion with the administration of fructose in diabetic persons, although the blood and urinary fructose values remained comparable to those obtained in normal individuals.

The results of the investigations of Drucker and his associates[14] and of Elman[20] indicated a superior utilization of fructose over glucose in the period following operation. Drucker's studies were based on four-hour tolerance tests using 10 per cent solutions. Elman employed 2 L. infusions for four days, alternating the administration of fructose and glucose in 10 per cent concentration. Rosenthal and co-workers[24] investigated invert sugar in the period following operation, terminating the study six hours after the start of the intravenous injection. They found a greater retention of the invert sugar in contrast to glucose but were unable to demonstrate any increase in diuresis, the total urinary output being comparable in the two groups.

Further studies of the utilization of fructose in the period after operation seem indicated. The decrease in glucose tolerance following operation varies considerably from patient to patient and is often of little clinical significance.[3, 31] It would seem that any conclusion in this respect would require a larger number of studies because the degree of diminution in glucose tolerance varies and the length of time for this change is not constant. Such tests should cover twenty-four hour periods, for conclusions in this regard cannot be drawn from tolerance tests alone.

Utilization of Fructose and Glucose When Injected Into the Portal Venous System.—Cori and Cori[10] compared the utilization of fructose injected into the femoral vein with infusion into the mesenteric vein of the rat. They concluded that direct infusion into the mesenteric vein resulted in better utilization of the

hexose on the basis of determinations of the tolerance limits. They determined that the tolerance limit for fructose in the rat by mesenteric vein was 0.7 Gm. per kilogram per hour as compared with a tolerance limit of 0.35 Gm. per kilogram per hour by peripheral vein. Both values were below the tolerance of glucose.

In this connection Peters and Van Slyke[21] have stated: "When injected into a peripheral vein, it (fructose) can be utilized by man or rat only about one-tenth as rapidly as glucose. If it (fructose) is injected into the mesenteric vein, so that it must pass first through the liver, it is utilized at twice this speed. The evidence indicates that levulose (fructose) is usually transformed to glycogen or glucose before it is utilized."

There are certain obvious difficulties in applying this study to patients because an operative procedure is required to insert a suitable catheter into the portal venous system. Thus, such studies must by necessity be conducted in the postoperative period.

Three patients in our investigations have been subjected to laparotomy with insertion of polyethylene catheters into the portal venous system. Following operation, the patients received all intravenous therapy by this route for four days and were allowed no oral fluids or food.

The first patient was a 42-year-old white man with a solitary metastatic carcinomatous nodule in the right lobe of the liver. Liver function was normal according to multiple standard tests. Preparatory to resection of the portion of the liver containing the metastasis, laparotomy was performed and the hepatic artery ligated at its origin at the celiac artery. Good pulsation was felt distal to the ligature. A polyethylene catheter was inserted into the portal vein through an omental vein. For two days after operation, the patient received fluids containing 200 Gm. of fructose each day and then 200 Gm. of glucose daily for the following two days (see Table II). The other two patients were subjected to subtotal gastrectomy for duodenal ulcer, and a polyethylene catheter was introduced into the portal vein in a similar manner at the completion of the operation. Three hundred grams of fructose or glucose was given on alternate days in 10 per cent concentration (Table II). Methods employed in these studies have been adequately described elsewhere.[2, 4]

An analysis of the results of the study indicated that in two of the patients the excretion of glucose and fructose administered through a mesenteric vein did not differ significantly from the excretion of these hexoses when injected into the peripheral venous circulation. In one patient (T. M.) there did appear to be a significantly greater retention of sugar when the hexose sugars were injected into the portal venous circulation, although unfortunately studies were not conducted in this patient by infusion through the systemic venous circulation. In all three patients the retention of glucose was superior to fructose.

While the number of patients studied is not sufficient to establish conclusions in regard to the comparative utilization of infusion of sugar solutions by way of the systemic and portal venous routes, the results of excretion of

sodium and potassium appear to have greater importance. The loss of sodium and potassium was greater in the patients receiving fructose than was obtained with glucose infusions. This was noted on the day following operation as well as forty-eight hours later. This would appear to confirm the observations previously made concerning the diuretic effect of fructose solutions administered intravenously.

TABLE IIA. RESULTS OF INFUSION OF FRUCTOSE AND GLUCOSE SOLUTIONS INTO MESENTERIC VEIN

PATIENT	DAYS P.O.	HEXOSE (GM.)	URINE VOLUME (C.C.)	URINARY CONTENT		TOTAL URINARY SUGAR	Na (MEQ.)	K (MEQ.)
				GLUCOSE (GM.)	FRUCTOSE (GM.)			
T. M., M. 42	1	200 fructose	740	3.7	4.9	8.6	171	84
	2	200 fructose	875	3.1	3.8	6.9	167	85
	3	200 glucose	1,430	1.6	0.9	2.5	143	47
	4	200 glucose	1,496	2.0	0.04	2.04	140	51
E. F., M. 41	1	300 glucose	2,210	27.9	0.03	27.93	170	47.8
	2	300 fructose	3,490	20.4	19.5	39.9	173.8	67.9
H. G., M. 24	1	300 glucose	2,733	15.1	1.87	16.97	114.8	27.33
	2	300 fructose	2,987	11.69	16.84	28.58	179.2	89.6

TABLE IIB. INFUSION COMPOSITION ON A TWENTY-FOUR HOUR BASIS

PATIENT	6% PROTEIN HYDROLYSATE WITH 10% HEXOSE (C.C.)	10% HEXOSE (C.C.)	HEXOSE (GM.)	N_2 (GM.)	K (MEQ.)	Na (MEQ.)
T. M.	2,000	1,000	200	16	40	140
E. F.		3,000	300	0		
H. G.		3,000*	300	0	60	77

*Received 500 c.c. of normal saline solution in addition to 3,000 c.c. of hexose solution in distilled water, with added KCl.

DISCUSSION

The investigations of Chaikoff[8, 9] have contributed significantly to the understanding of the differences between metabolism of glucose and fructose. In extensive studies in vitro using liver slices from normal and diabetic organs, Chaikoff demonstrated that diabetic animal tissue has a decreased ability to convert glucose to CO_2 and fatty acids. Further investigations demonstrated that fructose was converted to glucose in normal livers and that this conversion was not impaired in diabetic liver slices. Furthermore, the oxidation of fructose to CO_2 did not differ significantly in the normal and diabetic liver, although there was impaired fatty acid synthesis with both glucose and fructose. It is thus apparent that fructose enters the glycolytic path at a point separate from that of glucose.

Cori[11] has shown that fructose is rapidly converted to glucose under aerobic conditions, but not under anaerobic conditions.

These findings are pertinent because the liver appears to be the organ principally involved in the metabolism of fructose. The question that has not been entirely answered is whether fructose is utilized by extrahepatic tissues.

It seems likely that fructose may be utilized to some extent in the absence of the liver. It has been demonstrated that fructose disappears from the eviscerated, nephrectomized rat and prolongs the survival of such experimental preparations.[22]

Bollman and Mann[5] found that the injection of fructose into animals following hepatectomy was followed by a rise in the glucose content of the blood and that symptoms of hypoglycemia were prevented. In neither instance, however, was fructose as effective as glucose.

Mammalian muscle readily transforms fructose into lactic acid.[16] However, muscle utilizes glucose and not lactic acid; so it is perhaps significant for this discussion that lactic acid may be converted to glycogen and thus to glucose by the liver.

The observations cited earlier in the paper that the intravenous infusion of fructose is associated with elevation of the blood glucose level as well as the blood fructose level suggest that perhaps at least part of the effectiveness of fructose may depend upon its conversion to glucose. This is supported by the observation of Miller[19] that fructose infusions in diabetic persons result in an increase in the excretion of glucose.

The marked loss of electrolytes associated with the injection of fructose appears to be related to low renal threshold for fructose. This correlates well with the low tolerance rate demonstrated by Woodyatt and associates.[31] Thus, at customary rates of infusion, fructose is administered in excess of the tolerance limit, which should increase the concentration of solute in the urine. Brodsky and associates[7] demonstrated that the pattern of urine flow is related to the total number of osmotically active particles being excreted by the kidney. The finding of a greater excretion of electrolytes in the urine with the administration of fructose than with glucose would lead one to suspect that a larger quantity of reducing sugar was being excreted. It is also possible that the excretion of the large quantities of acid radicals, for example, lactic acid, may contribute to the loss of sodium and potassium. In clinical application, the increased electrolyte loss associated with infusion of fructose seriously detracts from its usefulness, particularly in patients undergoing surgical procedures or suffering from fluid and electrolyte imbalance.

SUMMARY

Fructose disappears rapidly from the blood stream when injected intravenously in man. The infusion of fructose is associated with increases in the blood fructose and blood glucose levels. Although it has been reported that usually the rise in these blood levels is not as great as the rise in blood glucose after the administration of similar quantities of glucose, the rise in total blood sugar may be approximately the same following the intravenous administration of either hexose.

The injection of fructose is associated with marked increases in the blood levels of lactic acid, pyruvic acid, and alpha-ketoglutaric acid, which exceed that observed with the infusion of glucose.

The administration of fructose is followed by the excretion of definite quantities of both fructose and glucose in the urine. Mellituria continues for several hours after completion of intravenous infusion of the hexose. Recent evidence suggests that larger amounts of reducing sugars may be excreted when fructose is given than when equal amounts of glucose are administered.

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THE ROLE OF INTESTINAL BACTERIA IN LIVER NECROSIS FOLLOWING EXPERIMENTAL EXCISION OF THE HEPATIC ARTERIAL SUPPLY*

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EXCISION of the hepatic arterial supply in the dog results in death due to liver necrosis.[11, 13, 16, 20, 25, 31, 32] Since Wolbach and Saiki,[47] in 1909, first described the almost constant occurrence of an anaerobic sporebearing bacterium in apparently normal livers of healthy dogs, the bacillus has been regarded as being responsible for the infection and subsequent death that follows deprivation of arterial blood to the liver. In a previous study, the described anaerobic bacillus, which was identified as *Clostridium welchii*, was found to be present in the peritoneal fluid of dogs which survived the production of appendiceal peritonitis, and the organism was demonstrated to be nonpathogenic in those circumstances.[40] It was also shown that gram-positive cocci were primarily responsible for the lethal outcome of inadequately treated peritonitis. The results of that study stimulated investigation of the etiology of the lethal infection that follows excision of the hepatic arterial supply.

The objectives of this study were: (1) to determine the role of *Clostridium welchii* in producing necrosis of the liver following excision of the hepatic arterial supply, (2) to evaluate the roles of other bacteria, if any, that may be important in this process, and (3) to determine the site of origin of these bacteria.

MATERIALS AND METHODS

Maintenance of Dogs and Operative Procedure.—Adult mongrel dogs, both male and female, varying in weight from 6.6 to 15.7 kilograms, were used as subjects. All dogs were inoculated with canine antidistemper and antihepatitis serum at the time they were placed in our animal hospital, and they were kept under observation at least four weeks before they were employed in this study.

Anesthesia was produced with veterinary Nembutal sodium, 30 mg. per kilogram of body weight, administered intravenously. The abdominal area of the dogs was shaved and prepared with pHisoHex. An upper midline incision of the abdomen was employed. After the peritoneal cavity was entered, blood from the portal vein and a portion of the liver were obtained for culture and assay studies. The portal vein was identified following a minimal amount of manipulation, and 10 ml. of blood was aspirated from the vein through a 22 gauge needle. A wedge of liver tissue was removed from the anterior surface of the left lobe of the liver. The common hepatic artery was identified, freed

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from the accompanying sympathetic plexus, and traced to its origin at the celiac axis or abdominal aorta, at which site it was doubly ligated and divided. The vessel was then dissected along its entire course from that level to its termination in the posterior superior pancreaticoduodenal and right gastroepiploic arteries. The three to five hepatic proper arteries which arise from the common hepatic artery and enter the liver at its hilus were carefully identified, dissected free, ligated, and divided. The right gastric artery was also ligated and divided, and the entire common hepatic artery and its branches were excised. The areolar tissue in the vicinity of the portal vein and common bile duct was excised, and all small vessels in this region were ligated and divided. All attachments of omentum to the liver were severed. The gall bladder was then removed because it has been reported that perforation of the organ may occur following excision of the hepatic artery.[20, 44] The abdominal wall was closed in two layers. Each dog was given 50 ml. of 5 per cent dextrose in distilled water per kilogram of body weight intravenously during the operative procedure.

Antibiotic and Supportive Therapy.—Neomycin* was the antibiotic selected for use in this study because administration of the drug results in almost complete sterilization of the gastrointestinal tract, and there is very little absorption of the antibiotic into the systemic circulation following oral ingestion.[35, 36, 41] Also, it has been reported that neomycin has no effect on the growth of *Clostridium welchii* in vivo or in vitro[41]; it therefore fulfilled all the requirements for use in this investigation.

Twenty-five dogs in this study received neomycin therapy, and twenty dogs which received no antibiotic therapy served as controls. The neomycin-treated dogs did not receive any other antibiotic therapy. All neomycin was administered orally, a dose of 0.1 Gm. per kilogram per day being given in two divided doses for two days before operation. Sixty milliliters of castor oil was given through a stomach tube at the time of the initial dose. The dogs were given water ad libitum during this two-day period of preoperative preparation, but they were not given any other liquids and no food orally. Twenty-five milliliters of 50 per cent dextrose was given intravenously twice daily during this period. The same regimen of neomycin administration was continued the day of operation and for two days thereafter. The dogs received nothing by mouth other than neomycin tablets during the first two postoperative days. They received parenteral fluids subcutaneously and/or intravenously, the total amount of fluid being based on each dog's body weight. In order to avoid any undesirable fluid or electrolyte shifts, the only fluid administered subcutaneously was normal saline solution.[1] Twenty-five milliliters of 50 per cent dextrose was given intravenously twice daily to dogs not receiving dextrose in other intravenous fluids. Five per cent dextrose in normal saline solution was employed as fluid for intravenous administration. The dogs were given food and water ad libitum on the third postoperative day. Animals comprising the control group were given food and water until twenty-four hours before operation; they were given nothing by mouth from that time until the third postoperative

*Neomycin was kindly supplied by The Upjohn Company, Kalamazoo, Michigan.

day. During that period the control animals received the same regimen of fluid and electrolyte supportive therapy as was given the neomycin-treated dogs.

Culture and Sensitivity Determination Methods.—Peritoneal fluid was obtained for culture by introduction of a needle into the right upper quadrant of the abdomen and aspiration of at least 5 ml. of fluid. The fluid was centrifuged, and the sediment used for culturing. Each specimen thus obtained was streaked on Endo and blood agar media, and then incubated; one blood agar plate was placed under anaerobic conditions. All plates were examined after overnight incubation, and organisms were identified. Peritoneal fluid was obtained for culture twenty-four hours postoperatively and then every twenty-four hours for the next two days. Peritoneal fluid was also cultured on the fifth postoperative day, and then every second or third day, as long as it could be obtained by paracentesis. No fluid obtained at post-mortem examinations was cultured. Blood was obtained from jugular veins, and the schedule of culturing was the same as that for peritoneal fluid. Blood obtained from the portal vein at the time of operation and from peripheral veins postoperatively was cultured aerobically and anaerobically in tryptose broth* and Brewer thioglycollate medium.†

Specimens of liver taken at the time of operation were divided into two approximately equal portions. One portion was cut into fine pieces and placed directly in Brewer thioglycollate medium, and the other was macerated under aseptic conditions and streaked on Endo and blood agar media.

The fecal flora of all dogs was examined before neomycin was administered, on the morning of operation, and, in some instances, two or three days after the termination of therapy. Fecal colony counts were performed by homogenizing 1 Gm. of wet feces with 20 ml. of normal saline solution, making serial tenfold dilutions of the specimen, and then evenly distributing 0.1 ml. of each dilution on the surface of blood agar plates. The inoculated plates were incubated aerobically and anaerobically.

Many strains of clostridia cultured from peritoneal fluid, blood, and stool specimens were isolated in pure culture, and a test for lecithinase, as described by Nagler,[34, 40] was performed.

Organisms cultured from the peritoneal fluid and blood of dogs receiving neomycin were isolated in pure culture, and the in vitro sensitivity of the bacteria to neomycin was ascertained by a serial tube dilution method.[40] The highest concentration of neomycin used in these determinations was 500 μg per milliliter; serial dilutions were made to the lowest concentration of 0.4 μg per milliliter. The neomycin used for testing was inoculated in 0.5 ml. quantities with 0.5 ml. of a 10^{-3} dilution of an eighteen-hour broth culture of the organism to be tested. The tubes were examined after overnight incubation; complete inhibition of growth was selected as the end point.

*Made by Digestive Ferments Company.
†Made by Baltimore Biological Laboratories.

Determination of Neomycin Levels.—A dose of neomycin was given at varying intervals before each operation, and portal vein blood was obtained at the time of operation for assay of the neomycin content. At the same time blood was obtained from the portal vein, it was also obtained from a jugular vein for neomycin assay. Peripheral blood was obtained for assay at other varying intervals following ingestion of doses of neomycin. The assay method is one in which there is serial dilution in tryptose broth of the initial sample of plasma placed in the first tube. After dilution, 0.5 ml. quantities remaining in each tube are inoculated with 0.5 ml. of a 10^{-3} dilution of an eighteen-hour broth culture of the Smith strain of *Staphylococcus albus*. The tubes were examined after overnight incubation. A standard using neomycin was prepared every time samples were assayed. After determination of the end point of the standard, the concentration of neomycin in the sample was calculated.

RESULTS

Forty-five dogs in which the hepatic arterial supply was excised are included in this study. Twenty-five animals received oral neomycin therapy, and twenty served as controls. No dog that survived less than twenty-four hours postoperatively was included in either series. All other dogs that were operated upon were included in this study, regardless of the cause of death. The mortality rate and length of survival of dogs in each group are shown in Fig. 1. The period of observation was twenty-one days; each dog which survived that long was sacrificed and autopsied at that time.

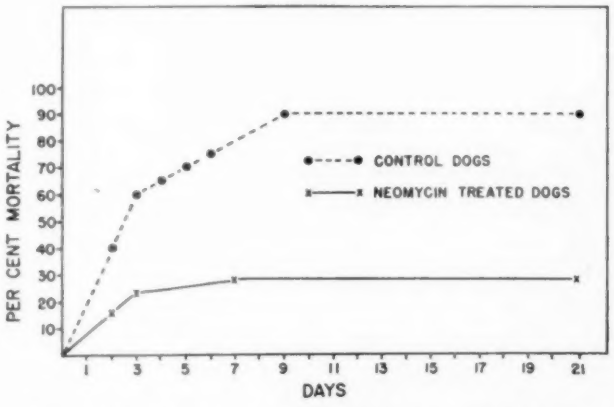

Fig. 1.—Mortality rates of treated and control dogs.

There was little difference in the clinical courses of any of the animals that died. After those dogs recovered from the anesthetic, there followed a variable period of time in which they appeared well. This phase was followed by hyperthermia, vomiting, progressive lethargy, and death.

Few of the neomycin-treated dogs which survived went through a period of crisis. Almost all of them did well from the time they recovered from the anesthetic, and they appeared to be in excellent health during the twenty-one-day observation period. Four of the treated dogs that survived did become jaundiced

day. During that period the control animals received the same regimen of fluid and electrolyte supportive therapy as was given the neomycin-treated dogs.

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The fecal flora of all dogs was examined before neomycin was administered, on the morning of operation, and, in some instances, two or three days after the termination of therapy. Fecal colony counts were performed by homogenizing 1 Gm. of wet feces with 20 ml. of normal saline solution, making serial tenfold dilutions of the specimen, and then evenly distributing 0.1 ml. of each dilution on the surface of blood agar plates. The inoculated plates were incubated aerobically and anaerobically.

Many strains of clostridia cultured from peritoneal fluid, blood, and stool specimens were isolated in pure culture, and a test for lecithinase, as described by Nagler,[34, 40] was performed.

Organisms cultured from the peritoneal fluid and blood of dogs receiving neomycin were isolated in pure culture, and the in vitro sensitivity of the bacteria to neomycin was ascertained by a serial tube dilution method.[40] The highest concentration of neomycin used in these determinations was 500 μg per milliliter; serial dilutions were made to the lowest concentration of 0.4 μg per milliliter. The neomycin used for testing was inoculated in 0.5 ml. quantities with 0.5 ml. of a 10^{-3} dilution of an eighteen-hour broth culture of the organism to be tested. The tubes were examined after overnight incubation; complete inhibition of growth was selected as the end point.

*Made by Digestive Ferments Company.
†Made by Baltimore Biological Laboratories.

Determination of Neomycin Levels.—A dose of neomycin was given at varying intervals before each operation, and portal vein blood was obtained at the time of operation for assay of the neomycin content. At the same time blood was obtained from the portal vein, it was also obtained from a jugular vein for neomycin assay. Peripheral blood was obtained for assay at other varying intervals following ingestion of doses of neomycin. The assay method is one in which there is serial dilution in tryptose broth of the initial sample of plasma placed in the first tube. After dilution, 0.5 ml. quantities remaining in each tube are inoculated with 0.5 ml. of a 10^{-3} dilution of an eighteen-hour broth culture of the Smith strain of *Staphylococcus albus*. The tubes were examined after overnight incubation. A standard using neomycin was prepared every time samples were assayed. After determination of the end point of the standard, the concentration of neomycin in the sample was calculated.

RESULTS

Forty-five dogs in which the hepatic arterial supply was excised are included in this study. Twenty-five animals received oral neomycin therapy, and twenty served as controls. No dog that survived less than twenty-four hours postoperatively was included in either series. All other dogs that were operated upon were included in this study, regardless of the cause of death. The mortality rate and length of survival of dogs in each group are shown in Fig. 1. The period of observation was twenty-one days; each dog which survived that long was sacrificed and autopsied at that time.

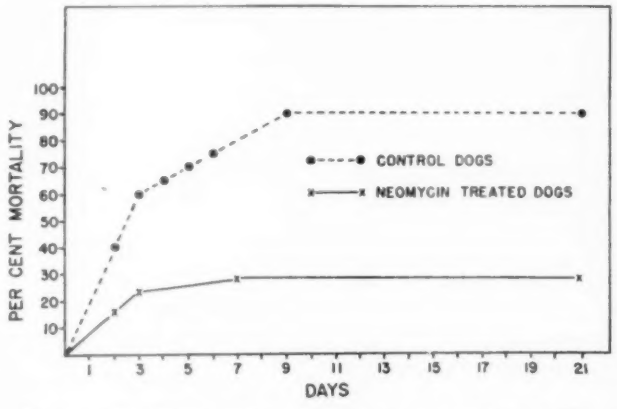

Fig. 1.—Mortality rates of treated and control dogs.

There was little difference in the clinical courses of any of the animals that died. After those dogs recovered from the anesthetic, there followed a variable period of time in which they appeared well. This phase was followed by hyperthermia, vomiting, progressive lethargy, and death.

Few of the neomycin-treated dogs which survived went through a period of crisis. Almost all of them did well from the time they recovered from the anesthetic, and they appeared to be in excellent health during the twenty-one-day observation period. Four of the treated dogs that survived did become jaundiced

postoperatively, but they had few symptoms during that period and appeared as well as the other surviving dogs. The jaundice, which could be detected clinically on the third or fourth postoperative day, cleared rapidly so that by the ninth day it could no longer be observed. At that time, serum bilirubin determinations also were found to be within normal limits. Serum bilirubin levels were determined in every dog on the fifth postoperative day and, if the values were elevated, repeated determinations were made. One of the two control dogs which survived twenty-one days became jaundiced on the third postoperative day and remained so until the twelfth day. The total serum bilirubin in that dog rose to 16.2 mg. per cent; that was the highest value found in this study. Unlike the previously mentioned treated dogs which became jaundiced, this dog had a postoperative course marked by continued anorexia, vomiting, and lethargy. The other control dog which survived had an uneventful postoperative clinical course.

Autopsies were performed on all dogs as soon after death as possible. There was little difference in the findings in any of the dogs that died, whether they had received neomycin therapy or not. There were varying quantities of gas and reddish black fluid in the peritoneal cavity, and all degrees of hyperemia and discoloration of the intestinal wall, mesentery, and visceral and parietal peritonea. The lobes of the liver varied in their gross appearance. In many dogs there were numerous areas of necrosis and abscess formation throughout the entire liver. In some instances, blebs of gas were found over the surface of most of the liver, and foam was present when the liver was sectioned. In a few dogs the liver had a uniform yellow color, but in most of them there were numerous areas of greenish purple discoloration. Histologic changes in the livers of these dogs varied from acute inflammation to necrosis of the parenchyma. Areas in which there was massive hemorrhage and abscess formation were frequently observed. Edema and necrosis of bile ducts with extravasation of bile were also seen.

Autopsy on the twenty-first postoperative day of the four neomycin-treated dogs that became jaundiced in the first week following operation revealed localized areas of abnormal hepatic architecture, but most of the liver appeared grossly and histologically normal in each of them. The most extensive involvement in these dogs was in one that had areas of necrosis in approximately 20 per cent of the right lobe of the liver; the remainder of the organ appeared normal. There was one other treated dog in which autopsy after twenty-one days revealed a small area of necrosis and abscess formation in the upper portion of the left lobe of the liver and no other gross or histologic changes in the remainder of the organ. That dog did not become jaundiced at any time postoperatively, and its serum bilirubin was within normal limits. All other neomycin-treated dogs that survived had normal findings at the time they were sacrificed; the livers of these dogs showed no evidence of disease, and the peritonea were glistening. The control dog that survived and had an uneventful postoperative course also had normal findings at the time it was sacrificed. The other sur-

viving control dog, whose course was marked by jaundice, anorexia, vomiting, and lethargy, had severe changes at autopsy. There were numerous areas of necrosis and abscess formation throughout the entire liver, and most of the organ had a greenish purple discoloration. The intestinal wall and peritonea were discolored and thickened, and there was extensive reaction in the right upper quadrant of the abdomen with numerous loops of intestine being adhered to the undersurface of the liver.

The distribution of bacteria isolated from the peritoneal cavities of control and treated dogs is shown in Table I. It can be seen that gram-positive cocci were isolated from only one of the twenty dogs that survived, and that one, which was in the control series, had extensive changes in its liver at autopsy. On the other hand, gram-positive cocci were isolated from nineteen of the twenty-five dogs that died. *Clostridium welchii* was isolated from nine of the surviving dogs and from seventeen of the dogs that died. With the exception of one of the two untreated dogs that lived, *Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa,* and *Clostridium welchii* were the only organisms isolated from any dog that survived as long as seven days. All clostridia that were isolated and tested were found to produce lecithinase and were therefore classified as *Clostridium welchii.*

TABLE I. DISTRIBUTION OF MICROORGANISMS ISOLATED FROM PERITONEAL CAVITY AND RELATIONSHIP TO SURVIVAL

ORGANISM	NO. OF DOGS IN EACH GROUP FROM WHICH THE SPECIFIED ORGANISM WAS ISOLATED			
	CONTROL		TREATED	
	DIED	SURVIVED	DIED	SURVIVED
Staphylococcus albus	13	1	4	
Nonhemolytic streptococci	8	1		
Escherichia coli	5	2	1	2
Proteus vulgaris	2	1		1
Pseudomonas aeruginosa	1			1
Clostridium welchii	14	2	3	7
No gram-positive cocci isolated	3	1	3	18
Total cases cultured	18	2	7	18

Positive blood cultures were obtained in twelve control dogs and five treated dogs. Eleven of the twelve control dogs and two of the five treated dogs died. Only one of several blood cultures was positive in each of the three treated dogs that survived, and only one organism was isolated in each case, a strain of *Pseudomonas aeruginosa* being isolated in one, *Proteus vulgaris* in one, and *Clostridium welchii* in the other. In each of these other dogs, repeated blood cultures were positive until the dog died or was sacrificed and, in ten cases, several species of organisms were isolated from each blood culture.

Positive portal vein blood cultures were obtained in twelve of the twenty control dogs. *Staphylococcus albus* and/or nonhemolytic streptococci were isolated in eleven of the twelve instances of positive cultures. Also, *Clostridium welchii* was isolated in three instances, *Escherichia coli* in one, *Pseudomonas*

aeruginosa in one, and yeasts in two cultures. There were no positive cultures of portal vein blood from treated dogs with the exception of one instance, in which yeasts were isolated.

Clostridium welchii was isolated from specimens of liver from ten of the twenty control dogs and ten of the twenty-five treated dogs when the liver was placed directly in Brewer thioglycollate medium at the time it was obtained at operation. Yeasts, which were isolated from one control and two treated dogs, were the only other organisms isolated from broth cultures of livers. When a specimen of liver was macerated, streaked on a blood agar plate, and then incubated aerobically and anaerobically, *Clostridium welchii* was cultured in only two control dogs and one treated dog. Except for yeasts, which were grown from the livers of one control and one treated dog when specimens were cultured in this manner, no other organisms could be isolated. In each of the instances in which these organisms were grown by the latter culturing method, the organisms were also demonstrated in thioglycollate broth cultures of a liver specimen from the dog. It can be seen that the incidence of positive cultures of *Clostridium welchii* was much greater when tissue was cultured in broth.

Examination of the fecal flora of treated dogs on the day of operation showed that all bacteria other than clostridia were cleared from the feces in sixteen dogs, and pure cultures of *Clostridium welchii* remained. The number of colonies of clostridia was not appreciably reduced during treatment in any dog. The following organisms were not cleared from the feces: *Pseudomonas aeruginosa* in seven instances, *Proteus vulgaris* in three instances, *Escherichia coli* in two instances, and *Aerobacter aerogenes* in one instance. All species of organisms reappeared in steadily increasing numbers in one to three days following cessation of therapy.

In vitro determinations of the sensitivity to neomycin of bacteria isolated from the peritoneal cavities and blood of treated dogs showed clostridia consistently to require high concentrations for inhibition. There were no instances in which a strain of *Clostridium welchii* was inhibited by less than 125 μg per milliliter. Each of the four strains of *Staphylococcus albus* that was tested was inhibited by 0.8 μg per milliliter or less, and each of the strains of *Escherichia coli, Proteus vulgaris,* and *Pseudomonas aeruginosa* was inhibited by 12.5 μg per milliliter or less.

Assay of the neomycin content of portal vein blood showed that the highest levels occurred one to one and one-half hours after ingestion of a dose. The highest level was 5 μg per milliliter, that value having been obtained in three of the twenty-five treated dogs. A level of 2.5 μg per milliliter was obtained in two dogs, 1.25 μg per milliliter in two, and all other levels were 0.625 μg per milliliter or less. The plasma level in blood that was drawn from the jugular vein concomitantly and at other times showed the highest level to be 2.5 μg per milliliter, that value being obtained in one instance. Levels of 1.25 μg per milliliter were obtained in four instances, and all other determinations gave values of 0.625 μg per milliliter or less.

DISCUSSION

The results of this study demonstrate that, in dogs, bacteria pass from the gastrointestinal tract to the liver via the portal vein. This was evidenced by positive cultures of portal vein blood in 60 per cent of apparently healthy nontreated dogs and negative cultures of portal vein blood in dogs in which the gastrointestinal tract was sterilized before the culture was obtained. It is interesting that whereas gram-positive cocci were isolated in 92 per cent of these positive portal vein cultures, gram-negative rods were isolated in only 17 per cent and *Clostridium welchii* in 25 per cent. This appears to indicate that the number of gram-positive cocci that pass the gastrointestinal barrier is greater than the number of gram-positive or gram-negative bacilli.

Prior to this study, it had not been established that portal vein blood contains bacteria and that there is seeding of the liver with bacteria from the intestine. However, these facts have seemed likely, since there have been several studies in the past which have shown that livers of fetal dogs are sterile and cause no toxic effects when placed in the peritoneal cavities of other dogs, whereas intraperitoneal implantation of livers from adult dogs results in death of the host dog unless the liver to be implanted is first sterilized by autoclaving. Following sterilization of the adult dog's liver, intraperitoneal implantation causes no ill effects.[6, 11, 16, 17]

The results of this study further show that, in dogs, continual passage of bacteria from the gastrointestinal tract to the liver plays a major role in death of the animals following excision of the hepatic arterial supply. This was evidenced by a mortality rate of 90 per cent in untreated animals as compared with one of 28 per cent in dogs in which the gastrointestinal tract was sterilized preoperatively with neomycin. Since neomycin therapy was given only two days postoperatively and the fecal flora returned in one to three days following cessation of therapy, explanation of continued survival of most of the treated animals must be that any deleterious effects of excision of the hepatic arterial supply were minimal in these dogs and return of an adequate physiologic function of the liver occurred within three to five days postoperatively. Sterilization of the intestinal tract allowed the liver to survive the borderline state of viability produced by deprivation of its arterial supply by preventing bacterial seeding of the liver and subsequent development of an overwhelming infection. After an effective collateral circulation formed in seventy-two to ninety-six hours, the liver recovered its normal function of bacterial filtration. Survival of intestine in which viability is borderline by prevention of bacterial proliferation and, conversely, necrosis of such tissues when infection occurs have been well demonstrated in the past by Blain.[8] Liver tissue is no different in that regard and, while ischemia following hepatic arterial ligation is the primary lesion, bacterial invasion of the ischemic organ is the decisive factor in determining necrosis. The fact that liver could be protected by neomycin therapy shows that widespread hepatic damage is not a necessary sequel to excision of the hepatic arterial supply.

The fact that there was no evidence in vivo or in vitro that neomycin had any effect on *Clostridium welchii* indicates that the organism does not play a significant role in death following excision of the hepatic arterial supply. Since fecal colony counts showed that the number of colonies of clostridia were not appreciably reduced in any dog by the therapy administered and the mortality rate of neomycin-treated dogs was greatly reduced, the primary factor must have been the effect of neomycin on other organisms present. Also, *Clostridium welchii* was cultured from the peritoneal cavities of 36 per cent and isolated from the broth cultures of livers of 32 per cent of the dogs that survived. These facts, along with the findings that there were positive cultures of *Clostridium welchii* from the peritoneal fluid of 68 per cent of dogs that died and there were varying quantities of gas in the abdomen and livers of many of these animals, indicate that the organism is essentially saprophytic and not pathogenic in liver tissue that is deprived of its arterial supply. Chau and his co-workers,[11] in attempting to show that the source of clostridial infection following hepatic artery ligation is the liver itself, gave dogs succinylsulfathiazole preoperatively, and *Clostridium welchii* was eliminated from the stools. However, other organisms were not eliminated, and all dogs died postoperatively. Since it has been shown by the results of this study that the elimination from the intestinal tract of organisms other than *Clostridium welchii* results in survival following deprivation of the hepatic arterial supply, the findings of Chau seem to substantiate the concept that clostridial organisms are of no primary importance in the development of hepatic necrosis and subsequent death of these animals.

The consensus that the livers of healthy dogs harbor a "normal" flora of *Clostridium welchii*[6, 8, 11, 19, 30-32, 39, 45] appears to be true in that the organism was isolated from broth cultures of liver specimens in 50 per cent of control dogs and 40 per cent of treated dogs. However, the fact that the organism could be grown in only 10 per cent of control dogs and 4 per cent of treated dogs when specimens of liver were macerated and streaked on blood agar plates indicates that the number of colonies per gram of liver tissue is small. The fact that no other organisms except yeasts could be grown even in broth cultures of liver tissue, despite the fact there were significant colony counts of organisms cultured from portal vein blood of the same dogs, indicates that organisms which enter the liver, with the exception of clostridia, are destroyed by phagocytosis in that organ.

It is easy to understand the reason *Clostridium welchii* has been thought to play a major role in hepatic necrosis and death of animals following excision of the hepatic arterial supply, since the organism does survive in pure culture in the liver of healthy dogs. The production of large amounts of gas and toxic products and ready demonstration of *Clostridium welchii* in dogs that die following hepatic arterial ligation[30] are explainable by the fact that the organism is a saprophyte. It is interesting that there have been no reports of survival of dogs that have undergone hepatic artery ligation following a building up of serum antilecithinase activity by intravenous injection of alpha toxin or following repeated administration of *Clostridium welchii* antitoxin.

An explanation of the existence of *Clostridium welchii* in pure culture in the liver is difficult because it does not seem likely that these organisms alone should pass the intestinal barrier, or that the liver would destroy all other organisms except clostridia. Trusler and his co-workers[45] have demonstrated that muscle of healthy living dogs also harbors an anaerobic flora, and Andrews and his associates[2] have shown that when any tissues of the dog become damaged there is extensive proliferation of *Clostridium welchii* because the organisms are present in the tissues at the time of injury. These latter workers concluded that the Welch bacillus is a normal inhabitant of all tissues of the dog.

Since, with the exception of one control dog, death occurred in all animals from which gram-positive cocci were isolated from peritoneal fluid postoperatively, it seems that these organisms play a major role in hepatic necrosis following excision of the hepatic arterial system. The surviving control dog from which gram-positive cocci were isolated in the peritoneal fluid postoperatively did have extensive changes in its liver and peritoneal cavity. This concept of the significance of gram-positive cocci is in keeping with previous findings that these organisms are most important in the production of peritonitis.[40] Gram-negative bacilli were isolated from the peritoneal fluid of several surviving dogs, as well as from dogs that died. There were several dogs from which few organisms, if any, were isolated, and it should be pointed out that the material cultured postoperatively was peritoneal fluid, and not liver tissue.

The fact that penicillin and Aureomycin afford protection to dogs following hepatic artery ligation is well documented.[15, 22-25, 37-39] It is interesting that streptomycin has been found to afford little or no protective action.[19, 24] All of the previously mentioned reports conclude that the beneficial results are due to the effect of the antibiotics on *Clostridium welchii*. It can be seen that the effectiveness of penicillin and Aureomycin, but not of streptomycin, could be well explained by the findings of this study that infection with gram-positive cocci is most important in determining liver necrosis following deprivation of the hepatic arterial blood supply. The mechanism of protection afforded by penicillin and Aureomycin differs from that of neomycin in that the action of the former antibiotics depends on attainment of adequate serum levels of the drugs in order to control liver tissue infection, whereas the beneficial effects afforded by neomycin depend on sterilization of the intestinal tract in order to prevent bacteria from reaching the liver and infecting the organ. The finding of the previously mentioned workers that penicillin need be given only a short time postoperatively is in keeping with our belief that the critical period of protection is within seventy-two to ninety-six hours postoperatively, after which time there develops in dogs which will survive an effective collateral circulation that enables the liver to resume its function as a bacterial filter.

An explanation of the survival of two control dogs following extensive excision of the hepatic arterial supply may be that preoperatively their hepatic arteries provided a small amount of the total blood flow and oxygen supply to the liver. The volume of blood and oxygen supplied by the hepatic artery

may also account for the hepatic necrosis and death that occurred in some of the treated animals; that is, in those cases, the hepatic artery may have supplied a larger amount of oxygen than it does in the average dog, and ligation may have resulted in immediate infarction of a large portion of the organ. Studies in unanesthetized dogs have shown that the volume of oxygen supplied by the hepatic artery varies from 22 to 62 per cent,[9] and similar studies in man have shown that the total flow of blood to the liver from the hepatic artery varies from 12 to 44 per cent and the volume of oxygen supplied varies from 20 to 62 per cent.[3] Another factor which influences survival following extensive excision of the hepatic arterial supply is the extent of the collateral circulation that develops subsequently. A wide variability in the direct and collateral blood supply of the dog's liver has been demonstrated to occur.[25, 29, 44] Marked differences in the hepatic artery flow and the collateral circulation of the liver also exist in other species of animals,[10, 43] and therefore it is difficult to extend the results of this work to other groups of animals. Behrend and his co-workers[4] operated upon dogs, cats, rabbits, and guinea pigs and found a varying susceptibility of these different species to hepatic artery ligation. He attributed the difference in mortality to the existing collateral circulation. It is known, for example, that the rat survives hepatic artery ligation. Some workers[22, 28] have stated that the rat's liver is less vulnerable to anoxia than the dog's liver because the normal rat's liver does not harbor bacteria whereas there is an anaerobic flora in the normal dog's liver. However, Wakim and Mann[46] have shown that the reason the rat survives hepatic artery ligation is that small collateral arteries pass to its liver from several sources. Therefore, it may be that survival of the rat and other animals following hepatic artery ligation is due to the existing collateral circulation and the amount of oxygen normally supplied by the hepatic artery, and not to a difference between those animals and the dog with regard to seeding of the liver with bacteria from the intestinal tract. It would seem that portal vein blood must be cultured in each of these species before it is known whether a different process exists in dogs than is present in the previously mentioned animals. It may be that a similar process of passage of intestinal bacteria to the liver exists in all, and inability to demonstrate any organisms in the livers of some animals is due to destruction by phagocytosis of all organisms as they reach the liver.

Although it has not yet been proved, there are many facts which strongly suggest that there is a similar process of seeding of the liver by intestinal bacteria in man. Several workers have concluded that the normal human liver does not harbor bacteria,[38, 39] although others[33] have demonstrated that a Welch-like bacillus can be cultured from human livers. Prior to the widespread use of antibiotics, there were many cases reported in which hepatic artery ligation in man was followed by liver necrosis and subsequent death.[5, 21, 27] On the other hand, there have been numerous reports of successful hepatic artery ligations in man when vigorous antibiotic therapy has been employed.[7, 37, 42] It follows, therefore, that bacteria may play a significant role in hepatic necrosis that occurs following deprivation of the arterial supply. Since there is no

endogenous liver flora, bacteria must reach the liver from other sources. It seems likely that this source in man is the gastrointestinal tract, and the portal vein is the route by which bacteria enter the liver, but this site of origin and portal of entry can only be proved by adequate cultures of portal vein blood. Since bacteria that enter the normal liver are destroyed by phagocytosis, one would expect cultures of liver tissue to show no growth.

It has been shown that, in man, antibiotics are of definite value in the treatment of acute and chronic diseases in which there is hepatic insufficiency.[18, 23] The fact that changes are usually more severe in the left lobe of the liver in cases of acute hepatic necrosis[18] is especially interesting because there is a selective distribution of portal blood in the liver and the left lobe receives blood from the colon, the site of greatest bacterial growth.[12, 26] All these findings support the concept of passage of bacteria from the intestinal tract to the liver via the portal vein in man and, if this is true, it provides a rationale for sterilization of the gastrointestinal tract in all cases of hepatitis, regardless of the cause.

SUMMARY

1. Excision of the hepatic arterial supply was performed in forty-five dogs. Twenty-five were treated with orally administered neomycin, and twenty were given no antibiotic therapy. The mortality rate of the neomycin-treated dogs was 28 per cent, whereas the mortality rate of the control dogs was 90 per cent. Since neomycin was poorly absorbed from the gastrointestinal tract and therefore had little, if any, systemic effect, the mechanism of protection of the former group of dogs was sterilization of the intestinal tract prior to excision of the hepatic arterial supply.

2. In normal healthy dogs, there is continual seeding of the liver by bacteria that pass from the gastrointestinal tract to that organ via the portal vein. This process is responsible for the overwhelming infection and subsequent death that occurs in untreated dogs following hepatic artery ligation.

3. It was demonstrated that infection is the decisive factor in determining necrosis following deprivation of the hepatic arterial supply, and gram-positive cocci are the most important of the organisms that invade the ischemic liver in untreated animals.

4. *Clostridium welchii,* which survives in pure culture in the livers of some healthy dogs, is a saprophyte. The organism plays no role in the hepatic necrosis and subsequent death that follow deprivation of the hepatic arterial supply of dogs.

5. The possibility that there is a similar process of passage to the liver of intestinal bacteria via the portal vein in other species of animals and in man is discussed, and evidence which suggests that this process occurs in man is presented.

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THE USE OF WIRE MARKERS IN COOPER'S LIGAMENT HERNIA REPAIRS WITH ROENTGENOLOGIC STUDIES

Report of Seventy-two Herniorrhaphies

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MUCH time and effort is expended toward developing objective means of expressing or illustrating the results of clinical findings. In an effort to facilitate this endeavor, Doran and Lonsdale (1949) described a new method of evaluating the results in inguinal hernia repairs. They advocated the placement of silver wire knots at corresponding points along the edges of the two layers to be coapted so that each pair of wire knots lying in contact could be viewed under direct vision at the time of the hernia repair and subsequently visualized by roentgenologic examination at any period in the postoperative follow-up. These authors found a definite spread of the wire "markers" three to six months after operation in seven of ten Bassini repairs and in one of three Cooper's ligament repairs.

This evidence against the Cooper's ligament (Lotheissen-McVay) method was based on such a small number of repairs that it is of no statistical significance. However, because of our interest in this operation (Harkins, Szilagyi, Brush, and Williams, 1942; Harkins and Swenson, 1943; Harkins and Schug, 1947; and Harkins, 1949), we were immediately interested in applying the marker method of Doran and Lonsdale in a much larger series of cases. This paper summarizes our experience with the Cooper's ligament repair of inguinal hernias using stainless steel wire (28 gauge) markers as an adjunct in the follow-up studies of our patients.

The utilization of Cooper's ligament as the line of attachment for the fascial structures in the repair of femoral hernias was introduced by Lotheissen*** (1898). The anatomic studies of McVay and Anson (1949) provided the rationale for the application of this method of hernia repair to direct and certain types of indirect hernias.

A large proportion of our patients presented themselves with hernias of a complicated nature for which the Cooper's ligament repair is especially well suited. In August, 1949, we decided to utilize the wire marker method in a consecutive series as an aid in the postoperative follow-up of our patients. Our purpose was to correlate the clinical postoperative findings with any roentgenologic change in the fascial-ligamentous relationship, as evidenced by the

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wire markers placed at the time of surgery. Recurrence of a hernia on the side previously repaired without displacement of the wire markers would serve to identify the formation of a new fascial weakness above the line of attachment at Cooper's ligament or a herniation at the internal inguinal ring.

The details of the technique are those personally taught the surgical resident staff by the senior author, as described by him and Schug (1947). Briefly this includes the following:

1. Silk sutures are used throughout for the hernia repair.
2. Stainless steel wire (28 gauge) knots are used as markers in the edge of the conjoined tendon—transversalis fascia and Cooper's ligament.
3. Spinal anesthesia is preferred but general as well as local anesthesia are also used.
4. Special equipment includes only a No. 6 or 7 Mayo needle.

The operative technique is outlined in the following ten steps:

1. Exposure of the spermatic cord and opening of the indirect sac at the internal inguinal ring.
2. Intraperitoneal digital exploration of Hesselbach's triangle and the femoral ring.
3. Hoguet's maneuver (transposition of direct or femoral sacs into the indirect sac).
4. Internal purse-string closure of the indirect sac.
5. MacGregor's maneuver (plastic repair of the internal inguinal ring).
6. Relaxing incision of the internal oblique.
7. Attachment of conjoined tendon and transversalis fascia to Cooper's ligament (double strands of No. 0 black silk).
8. Closure of the external oblique aponeurosis.
9. Closure of Scarpa's fascia.
10. Closure of the skin.

Postoperatively, the patients are ambulatory within twenty-four hours unless limiting conditions exist.

The Cooper's ligament hernioplasty together with the previously described wire markers was used in 53 patients, 51 men and 2 women. The average age in this group was 56 years, with a range from 28 to 84 years.

This group of 53 patients had 19 right-sided hernias, 15 on the left, and 19 bilateral hernias, making a total of 72 hernia repairs. The 72 hernias repaired are further subdivided as follows:

Simple indirect hernia	32
Strangulated indirect hernia	4
Sliding indirect hernia	1
Simple direct hernia	21
Combined direct and indirect hernia	6
Recurrent hernia	6
Femoral hernia	2
Recurrent indirect hernia	4
Recurrent direct hernia	1
Recurrent femoral hernia	1

The follow-up studies of these hernias on a long-term basis are not entirely satisfactory since it is difficult to secure the cooperation of our patients regarding their return to the clinics. In addition, many of our patients are frank

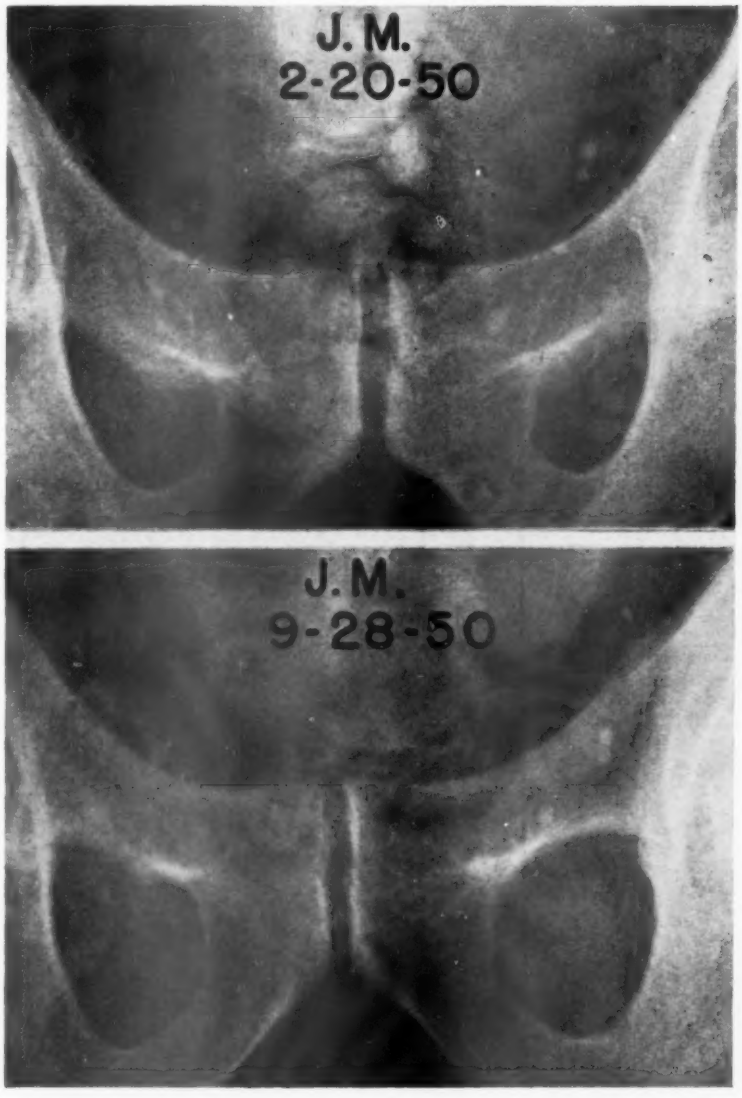
TABLE I. WIRE MARKER SEPARATION IN TEN COOPER'S LIGAMENT HERNIOPLASTIES

PATIENT AND HOSPITAL NUMBER	AGE (YR.)	TYPE OF HERNIA	SIDE	X-RAY STUDIES						
				CONTROL		FOLLOW-UP				
				DATE	X-RAY PROJECTION	DATE	X-RAY PROJECTION	WIRE MARKER DISPLACEMENT* (MM.)	FOLLOW-UP INTERVAL (MO.)	COMMENTS
L. H., 252865	73	Simple direct	Left	6-29-50	P-A	9- 6-51	P-A	6	14	Wire separated at 3 months
J. M., 30790	75	Simple indirect	Right	2-20-50	A-P	9-28-50	P-A	4	7	Early separation of markers with later hernia recurrence
M. K., 147145	68	Simple direct-indirect	Bilateral	11-10-49	A-P	2- 7-50	A-P	6	3	On left side only
G. M., 98083	84	Femoral	Right	7-25-50	A-P	6-25-53	P-A	34	35	Wound infected, shift possibly due to this
A. S., 35096	57	Simple direct	Right	5-27-50	A-P	9-14-51	A-P	9	15	Wires separated at 3 months
E. P., 110661	39	Simple indirect	Right	9-11-49	A-P	10-19-50	A-P	7	13	Wires separated at 3 months
J. M., 264740	74	Recurrent indirect	Right	7-24-50	A-P	10-19-50	P-A	6	3	Wound infected
E. G., 259771	61	Simple direct	Left	2- 2-50	A-P	4-13-53	P-A	12	38	Wire separation at last examination only
E. T., 1316	65	Simple indirect	Right	10-14-49	A-P	4-13-53	P-A	5	42	Wire separation at last examination only
L. D., 33283	31	Right—simple direct Left—recurrent indirect	Bilateral	8- 6-49	A-P	6-25-53	P-A	4	46	Late wire separation on left side only

*The lateral pair of wire markers showed separation in all these cases.

transients or indigents who move elsewhere to attempt to improve their economic status. The results of the follow-up of our patients in the clinic since August, 1949, are as follows:

A.



B.

Fig. 1.—*A*, An anteroposterior x-ray view of wire markers in right Cooper's ligament herniorrhaphy four days after operation in Patient J. M. Each of the pairs of markers is separated by 9 mm. (X-ray films retouched to accentuate appearance of wire markers.)

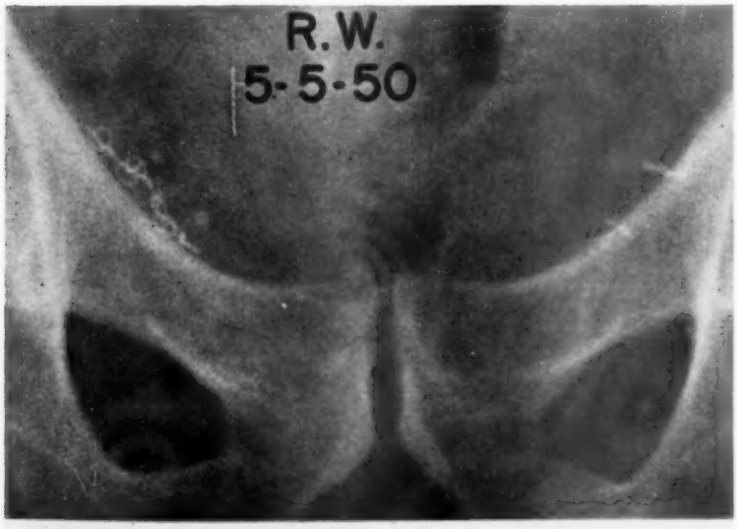
B, A posteroanterior x-ray view of the wire markers in Patient J. M. approximately seven months after operation showing the lateral markers with an additional displacement of 4 mm. This patient had a clinical recurrence of the hernia with the wire marker separation illustrated. (X-ray films retouched to accentuate appearance of wire markers.)

(a) Three months after operation: 45 hernias examined with 6 of these repairs showing separation of the wire markers but no evidence of recurrence to clinical examination. (n.b.—In all cases studied in this paper no separations occured of the medial markers; all separations noted were those of the lateral markers.)

(b) Six months after operation: 18 hernias examined and 1 additional case of wire marker separation detected. This latter patient (J. M.) also had clinical evidence of hernia recurrence.

(c) Nine months after operation: 11 hernia repairs examined with no additional cases of wire separation detected. One patient (N. P.) showed clinical recurrence of the hernia without change in the wire marker positions.

A.



B.

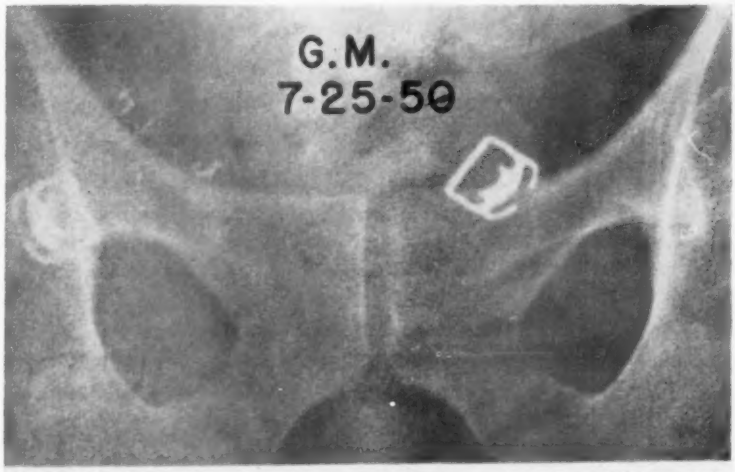
Fig. 2.—*A*, An anteroposterior x-ray view of wire markers in bilateral Cooper's ligament hernioplasties taken fourteen days after the left side was repaired and two days after the right-sided repair in Patient R. W.

B, A posteroanterior x-ray view of the wire markers in Patient R. W. approximately thirty-five months after the x-ray view shown in *A*. This patient had clinical recurrence of the indirect hernia on the left detected Sept. 6, 1951, and corrected on Oct. 9, 1951.

(d) Twelve months after operation: 13 hernias examined in the clinic with detection of 1 clinical recurrence but without displacement of the wire markers. This patient's clinical résumé is given later.

(c) Thirty-one to forty-six months (average thirty-eight months) after operation: 15 patients returned in this period presenting for examination 21 hernia repairs without any additional cases of clinical recurrence. It was possible to obtain x-ray examination of the hernia wire markers in 16 of these hernioplasties. Three additional cases of wire marker separation were detected.

A.



B.

Fig. 3.—*A*, An anteroposterior x-ray view of wire markers in a right Cooper's ligament hernioplasty taken six days after operation in Patient G. M. Note the position of lateral pair of wire markers.

B, A posteroanterior x-ray view of the wire markers in Patient G. M. obtained approximately thirty-five months after hernia repair. There is migration of one of the lateral markers to a medial position. No clinical recurrence of the hernia was detected at the last examination.

Table I gives the degree of wire marker separation observed in all the previously mentioned cases.*

The following are illustrative examples of the clinical findings and x-ray changes observed in the position of the wire markers in this series of patients.

*It is regrettable that many of the films taken in 1949 and 1950 were anteroposterior rather than posteroanterior as ordered. This was due to circumstances beyond our control.

1. *Clinical Recurrence of Hernia With Wire Marker Separation.*—J. M., Hospital No. 30790, a 75-year-old man, was operated upon on Feb. 16, 1950, for right indirect inguinal hernia of two weeks' duration. A postoperative x-ray examination on Feb. 20, 1950, revealed 9 mm. and 9 mm. separation of the medial and lateral pairs of wire markers, respectively (Fig. 1, *A*). A second examination of the markers three months postoperatively showed no change in their relative positions, while another x-ray examination seven months after operation showed that the lateral wire markers were separated by a distance of 13 mm. with no change in the positions of the medial markers (Fig. 1, *B*). The patient developed clinical signs of a recurrent hernia in December, 1950, with the defect being present in the region of the internal inguinal ring. Reoperation was advised, but the patient did not return and died later of other causes.

2. *Clinical Recurrence of Hernia Without Wire Marker Separation.*—R. W., Hospital No. 85325, an 81-year-old man, had bilateral simple indirect inguinal hernias. Repair of the left side was carried out April 21, 1950, and of the right side on May 3, 1950. X-ray examination was made in the interval between the two operations, and the position of the wire markers on the left side was the same as shown in Fig. 2, *A*, wherein both sides show wire markers. This patient was found to have a clinical recurrence on Sept. 6, 1951, which was not present on a previous clinic visit in October, 1950. The left inguinal region was re-explored on Oct. 9, 1951, with the finding of an indirect hernial sac 10 cm. long and 3 cm. in diameter. The operative note stated that it was felt that the recurrence was due to a dilated internal ring, possibly as an inadequate closure at the previous surgery, or possibly due to poor tissue in the area at the previous repair. Hesselbach's triangle was strong except at its lateral edge at the time of the re-exploration. This patient was last examined in clinic on April 13, 1953, with no clinical recurrence of either hernia. X-ray examination made on the last clinic visit (Fig. 2, *B*) showed the wire markers in essentially the same position as on May 5, 1950 (Fig. 2, *A*).

3. *Separation of Wire Markers Without Recurrent Herniation.*—G. M., Hospital No. 98083, an 84-year-old man, was operated upon on July 19, 1950, for a right femoral hernia. The postoperative position of the wire markers is shown in Fig. 3, *A*. The markers remained in the same relative positions on examination twelve months after operation. However, the most recent x-ray examination, made thirty-five months after repair of the hernia, shows migration of one of the lateral markers to a medial position (Fig. 3, *B*). This may be related to the development of a chronic draining inguinal sinus in the past year from which a strand of heavy black silk was obtained. There was no clinical evidence of recurrence of the hernia.

4. *No Separation of Wire Markers and No Hernia Recurrence.*—A majority of the hernia repairs which came to follow-up clinics are in this group.

SUMMARY

The method of Doran and Lonsdale of utilizing wire markers to detect separation of coapted fascial layers following herniorrhaphy was used in a series of 72 Cooper's ligament hernioplasties. Present follow-up studies indicate one definite clinical recurrence of a hernia supported by roentgenologic evidence of wire marker separation. In addition, there were two hernia repairs which showed suggestive evidence of clinical recurrence either as a weakness of the transversalis fascia above the site of repair or a recurrent herniation through the internal inguinal ring, but neither case showed a change in the position of the markers during the follow-up period.

In the total of 72 hernia repairs, there were 10 instances of wire marker separations, and only 1 of these separations (10 per cent) was associated with a recurrence of a hernia. In the remaining 62 repairs without marker separation there were 2 recurrences (3 per cent).

CONCLUSIONS

1. In this series of 72 Cooper's ligament hernioplasties in which wire markers were used as suggested by Doran and Lonsdale, there have been, at the last follow-up period, the following findings:

(a) One clinical recurrence of the hernia associated with separation of wire markers.

(b) Two cases of clinical recurrence (1 of which was questionable) without evidence of wire marker separation.

(c) Nine hernia repairs with displacement of the wire markers but without clinical evidence of recurrent herniation.

2. There appears to be slight but statistically insignificant correlation between the clinical recurrence of a hernia after its repair and the separation of wire markers placed in the edges of the transversalis fascia as well as in Cooper's ligament at the time of the operation.

3. In this series (72 hernioplasties) we have had 3 recurrences to date (4 per cent) (7 per cent of 43 hernioplasties followed six months or more) as compared to 1 recurrence in 3 Cooper's ligament hernioplasties (33 per cent) reported by Doran and Lonsdale. On the basis of the combined two series of 75 hernioplasties, the wire marker technique shows a low incidence of wire marker separation associated with clinical recurrence following the Cooper's ligament type of repair.

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PRIMARY DIRECT INGUINAL HERNIOPLASTY

A Study of 275 Cases

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A STUDY of the recurrence rates for the repair of primary direct inguinal hernias reveals, without a doubt, a much higher rate than that for an indirect inguinal hernioplasty.[2] This can be easily explained in the basic differences in the etiological and anatomic factors involved. Failures in the past are a result of innumerable factors, these being primarily an inadequate knowledge on the part of the surgeon of the basic anatomy of this area and the failure by the operator to provide proper reinforcement of the area of Hesselbach's triangle by the strong supporting structures of both the transversalis fascia and aponeurosis of the internal and external oblique muscles.

It is important, too, not to overlook the existence of an indirect inguinal hernia and to take the necessary steps to repair this associated defect. It is our purpose in this presentation to deal exclusively with the acquired defect, a direct inguinal hernia. It is important also to recognize the fact that in a high percentage of cases, particularly in patients over 35 years of age, a combination of both types of hernia may exist simultaneously.[10, 11]

A recent survey of the literature revealed a marked variation in the recurrence rates of a direct hernia, the average being 13 per cent.[1-9, 12-14] The various series reported revealed the recurrence range to vary from a low of 1.14 per cent to a high of 32 per cent.[8, 13]

Considerable disagreement exists as to the manner in which these defects should be repaired. However, in the past several years most authorities have discarded ox fascia, autogenous fascial strips, or grafts. Some continue to advocate the use of tantalum mesh, or a fascial or an aponeurotic patch. Others recommend and use the ligament of Cooper repair. All of these methods have failed consistently to reduce the recurrence rates within reasonable bounds.

Those who have had a great deal of experience in this field strongly urge the use of fine nonabsorable sutures, careful handling of tissues in order to minimize fibrosis, the placement of sutures without tension, and the utilization of the basic anatomy as it exists in each specific case without the use of muscle anywhere in the repair.

During the past fifteen years we have employed the same basic anatomic repair in all of the direct inguinal hernias. This report is based on a recent study of 275 primary direct inguinal hernioplasties performed upon 239 unselected and consecutive male patients during the past six years. In thirty-six

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(15.5 per cent), the hernias were bilateral. In none of the cases was a bilateral repair performed simultaneously. The opposite side was repaired between the seventh and tenth postoperative days.

The same basic technique was utilized in all cases, using fine nonabsorbable sutures, either silk or cotton. These operations were performed by thirty different members of the full-time and house staffs; however, most of the operations were performed by the latter group.

AGE INCIDENCE

The ages ranged from 19 to 76 years, with the largest number occurring in the 50-to-59-year group (42.3 per cent).

Ten per cent of the patients were 60 years of age or older (Table I).

TABLE I. HERNIA INCIDENCE ACCORDING TO AGE

AGE GROUP	NUMBER	PER CENT
Under 20	1	0.4
20-29	43	18.0
30-39	32	13.4
40-49	38	15.9
50-59	101	42.3
60-69	20	8.4
Over 70	4	1.6
Total	239	100.0

The hernias were divided almost evenly between the two sides (Table II).

TABLE II. LOCATION OF DIRECT HERNIA

SIDE	NUMBER	PER CENT
Right	143	52
Left	132	48
Total	275	100

In thirteen (5.4 per cent) patients, additional operations were performed at the time of hernioplasty (Table III).

TABLE III. OPERATIONS AT TIME OF HERNIOPLASTY

TYPE	NUMBER
Epigastric hernioplasty	1
Femoral hernioplasty	2
Hydrocelectomy	1
Lipoma of chest wall, excision	1
Lipoma of cord, excision	2
Neuroma of peroneal nerve, excision	1
Orchidectomy	1
Varicocelectomy	4
Total	13

OPERATIVE TECHNIQUE

It is our opinion that the hernia sac should be completely and carefully dissected from all of the surrounding structures, including its separation from the urinary bladder and then excision of the sac. The complete removal of the

sac is an important part of any hernia procedure since it represents the plunger or piston action which pushes itself through a weakened and deficient abdominal wall. The neck of the sac is closed by a purse-string suture of No. 00 or 000 silk. If the sac is large, the neck is closed by interrupted fine sutures.

Our basic repair consists of rebuilding and fortifying the weakened area in Hesselbach's triangle by a four-layered technique. This repair, with illustrations, has been described and portrayed elsewhere.[10, 11]

The first line of defense, and one which we consider an extremely important one, is the imbrication of the transversalis fascia by the use of at least three interrupted sutures of No. 000 silk. This takes the slack out of this important structure. The most medial portion is sutured to the thickened bandlike portion that lies beneath the inguinal ligament. It is the senior author's opinion (L. T. P.) that many surgeons who claim they are performing a ligament of Cooper repair are actually mistaking this thickened portion of the transversalis fascia for the Cooper ligament and are suturing the layers of the anterior abdominal wall to it instead of the ligament of Cooper, which is much deeper. This mistaken identity indicates the valuable anchoring potentialities of this portion of the transversalis fascia.

The second layer of repair is provided by suturing the medial rolled edge of the internal oblique aponeurosis to the shelving edge of Poupart's (inguinal) ligament with interrupted No. 00 silk. The third and fourth layers consist of imbricating the divided medial and lateral leaves of the external oblique aponeurosis beneath the cord to the newly formed floor of Hesselbach's triangle. This provides a four-layered, fascia-aponeurotic fortification of this weakened area. The cord is partially transplanted subcutaneously.

The internal inguinal ring is also made snug by this method. The divided external oblique aponeurosis is closed by interrupted No. 000 silk above the cord.

DEATHS

There was one postoperative death, a mortality of 0.3 per cent. This occurred in a 71-year-old white man on the eighth day as a result of bilateral femoral emboli and coronary occlusion.

RESULTS

A one- to six-year follow-up was obtained in 89.4 per cent (215) of patients, representing 248 operations. Ninety per cent were followed for two years or longer. It appears from a review of the literature that the majority of recurrences develop during the first two years. In view of this, we are of the opinion that the analysis of our results is statistically sound.

RECURRENCES

There were no direct recurrences in this group. In 247 of the operations followed, five patients (2 per cent) developed indirect hernias. The indirect hernias occurred in two patients under 40 years of age and three in patients in

the sixth decade. Two developed during the first year, two within the second year, and the fifth at the end of the third year; 80 per cent developed within a two-year period.

Ninety per cent of the operations were performed under spinal anesthesia, and the remaining number under general anesthesia.

EFFECTS OF EARLY AND LATE AMBULATION

A carefully controlled program was instituted at the inception of this study to determine the effects of early and late ambulation on the postoperative complication and recurrence rates. In all groups, the patients were unselected and represented consecutive cases. The patients ambulating late, on the seventh or fourteenth postoperative day, included sixty-eight patients (seventy-three hernioplasties), whereas 171 patients (202 hernioplasties) were ambulatory on the first postoperative day. In the late ambulatory group, the postoperative complication rate was 12.2 per cent, as compared to 4.5 per cent in the early ambulatory group (Table IV). The indirect hernias developed in 1.3 per cent of the late group, as compared to 2 per cent in the early group.

The over-all complication rate was 6.9 per cent.

TABLE IV. POSTOPERATIVE COMPLICATIONS

TYPE	LATE AMBULATORY GROUP	EARLY AMBULATORY GROUP	TOTAL
Pulmonary			
Atelectasis and/or pneumonia	2	2	4
Wound			
Infection	2	2	4
Hematoma	2	2	4
Miscellaneous	3	4	7
Total	9 (12.2%)	10 (4.5%)	19 (6.9%)

Forty-two per cent of the total complications occurred in the wound.

Our patients were instructed to refrain from heavy lifting, straining, or athletics for a period of six to eight weeks postoperatively. They were permitted to return to a sedentary type of work at the end of two weeks.

SUMMARY AND CONCLUSIONS

An analysis of the results of 275 primary direct inguinal hernioplasties performed upon 239 unselected and consecutive male patients with a follow-up of one to six years in 89.4 per cent of this series is presented.

There were no direct recurrences. Five patients developed indirect hernias within a three-year period. There were nineteen (6.9 per cent) postoperative complications, of which eight (2.9 per cent) involved the wound. There was a definite reduction in the incidence of complications dependent upon the day of ambulation. In the group of patients ambulatory on the first day, the complication rate was about one-third less frequent than in the group ambulatory late; in the former, it was 4.5 per cent and in the latter 12.2 per cent.

It appears from these studies that early ambulation effected a marked reduction in the postoperative complications without the development of a recurrence of the direct hernia. This policy also aided in a more rapid rehabilitation of the patient, resulting in great economic savings to the hospital and to the patient.

The absence of any direct recurrences in this consecutive group of patients in all age groups indicates that the basic technique of complete and careful dissection of the hernia sac, use of fine nonabsorbable sutures, atraumatic dissection, imbrication of the transversalis fascia, and reinforcement of the weakened area in Hesselbach's triangle by suturing the aponeurosis of the internal oblique to the shelving edges of the inguinal ligament and imbricating the medial and lateral leaves of the external oblique aponeurosis beneath the cord is a sound anatomic and physiologic approach to the problem of direct hernioplasty.

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FEMORAL HERNIAS IN INFANTS AND YOUNG CHILDREN

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FEMORAL hernias in infants and young children are rare. The diagnosis and operative repair of such hernias can be accomplished safely and adequately despite the fact that the patient may be extremely young.

INCIDENCE

Reports in the literature agree that femoral hernias are uncommon in children.[1, 2, 4, 7, 8] Rutherford reported a series of 1,098 cases in which operations for hernia were performed in children; 86 per cent of these hernias were inguinal, 13 per cent were umbilical, and 0.4 per cent (five) were femoral. A review of the operative cases at the Mayo Clinic for a ten-year period from 1941 through 1950 revealed one femoral hernia among 220 hernias of the groin in children 5 years of age or less. In addition, two other femoral hernias in identical male twins 2½ years of age were repaired by us in 1953.

So few cases have been reported that a predominance of such hernias in females, as is seen in the adult, would be difficult to determine in children. In 1926, Fraser wrote that he had never seen an instance of femoral hernia in a male child. Watson, however, considered that the sex incidence was equal in these young patients.

DIAGNOSIS

The diagnosis of femoral hernias in children, as in adults, is not difficult, but careful examination and the realization that all hernias of the groin in children are not necessarily inguinal are essential in the avoidance of errors. In infants and children, on occasion one must advise operation because of a history of a bulge that appears with crying or straining but that is not evident at the time of examination. Under such circumstances, it is important to ascertain the exact location of this bulge so that the presence of a femoral hernia may be suspected and thus not overlooked at the time of operation.

Harris reported a case of a strangulated femoral hernia in a child. This emphasizes the potential danger of these hernias, even in children, a point that argues for their repair as soon as the diagnosis is made.

OPERATIVE REPAIR

Cure of indirect hernias in infants and small children requires only high ligation of the sac[10]; meddlesome repairs of the posterior wall of the canal are

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to be avoided. Contrariwise, true repair is indicated in cases of femoral hernia, and this can be carried out in extremely small patients.

A transverse incision is made in the lowermost fold of the skin of the groin (see Fig. 1). The aponeurosis of the external oblique muscle of the abdomen is opened through one external inguinal ring. The spermatic cord is not mobilized but is displaced enough so that the transversalis fascia of the posterior wall of the inguinal canal is exposed. This is incised over the femoral hernia. The sac is then teased out from under the inguinal ligament and opened; any contents are replaced in their correct location. A high ligation of the peritoneal sac is performed. The repair is effected by suture of the transversalis fascia to Cooper's ligament out to the femoral vein. From this point laterally, the transversalis fascia is sutured to the femoral sheath to complete the repair.[9] Interrupted No. 00000 silk sutures swedged on an atraumatic needle serve admirably for the delicate stitching required for accurate apposition of these

Fig. 1.—Incision for repair of femoral hernias in infants and small children.

tissues. The spermatic cord is allowed to fall back to its normal position, and the aponeurosis of the external oblique muscle is reconstructed. The subcutaneous and subcuticular tissues are closed with interrupted, extremely fine, silk sutures after the method of Gross; cutaneous sutures are avoided. A thin coat of collodion is applied over the wound.

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Case Reports

THROMBOENDARTERECTOMY FOR LOCALIZED OCCLUSION OF THE TERMINAL AORTA

A Case Report: Re-enforcement of the Aortic Wall With a Skin Graft

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Leriche[1] in 1940 emphasized thrombosis of the terminal aorta as a cause of arterial insufficiency in the lower extremities and suggested bilateral lumbar sympathectomy in the treatment of this condition. Resection of the thrombosed segment of the aorta was also recommended whenever possible to prevent propagation of the thrombus and to relieve the attending low-back pain. The results obtained in this type of treatment have been reported by Elkins and Cooper,[2] Ortner and Griswold,[3] Beaconsfield and Kunlin,[4] and others.

Oudot and Beaconsfield[5] reported five cases of thrombosis of the aortic bifurcation successfully treated by resection and replacement with vascular homografts. Five similar operations have been successfully performed by Julian and his co-workers.[6] The operation was performed in three of their cases for aortic occlusion and in two others for aneurysm. Aortic resection with graft replacement for aneurysm has been described recently by several authors including Dubost, Allary, and Oeconomos,[7] DeBakey, and Cooley,[8] and Bahnson.[9]

Dos Santos'[10] method of thromboendarterectomy has been utilized in the treatment of terminal aortic thrombosis by Bazy,[11] Lemaire,[12] Wylie,[13, 16] Julian,[14] Barker,[15] and others.

Wylie[13] introduced the technique of applying a fascia lata graft to the weakened aortic wall to prevent postoperative rupture or dilatation of the vessel following thromboendarterectomy and aneurysmorrhaphy. The procedure was tested in experimental animals and subsequently utilized in the treatment of five patients.

We have recently treated a patient with thrombotic occlusion of the terminal aorta by thromboendarterectomy. The aortic wall was re-enforced by suturing a split-thickness skin graft about the weakened area. The simplicity and success of the procedure have prompted this report.

CASE REPORT

Arteriosclerosis With Thrombosis of Terminal Aorta.—

C. J., a 45-year-old white male master sergeant, was admitted to the hospital complaining of pain in both legs and in the back. In May, 1952, he was struck by a litter handle in the upper lumbar region during an airplane accident. Other than soft tissue contusion, there was no evidence of injury. Approximately two weeks later, while marching,

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he developed pain in the calf and thigh of both legs and in the lower back. The pain gradually subsided over a period of ten days. Following this, he regularly developed cramping pain in the calves, thighs, buttocks, and lower back upon walking more than one block or when climbing stairs. The pain was most severe during cold weather and was relieved by rest. He also complained that his feet were "cold all of the time."

The positive findings on physical examination included the following: (1) Vigorous pulsation of the upper abdominal aorta with complete absence of all arterial pulsations distal to the terminal aorta was noted. (2) The feet were cold, and subcutaneous veins filled slowly. (3) The blood pressure was 120 systolic and 84 diastolic (mm. Hg) in both arms. The blood pressure was unobtainable in the legs. (4) Oscillometric examination revealed no evidence of pulsations in either leg.

Fig. 1.—Retouched preoperative aortogram. Complete obstruction of aorta at level of fourth lumbar vertebra. Incomplete filling of iliac arteries.

A calcified area in the anterior wall of the distal aorta was identified in the lateral roentgenogram of the abdomen. A translumbar aortogram demonstrated a complete block in the aorta just above the bifurcation, with an irregular filling defect extending proximally along the right side of the lumen of the aorta to the level of the right renal artery. The patency of both iliac vessels was demonstrated (Fig. 1).

On Sept. 18, 1953, the abdominal aorta and iliac vessels were exposed. A long midline incision was used. The entire left half of the colon was mobilized and reflected to the right of the midline, exposing the aorta up to the level of the renal arteries and the iliac vessels for a distance 3 cm. distal to their origins. A hard calcified area 1½ cm. in diameter was palpated immediately distal to the origin of the inferior mesenteric artery. Above this area, the aorta was filled with a firm thrombus that was adherent to the right aortic wall and extended proximally to the origin of the right renal artery.

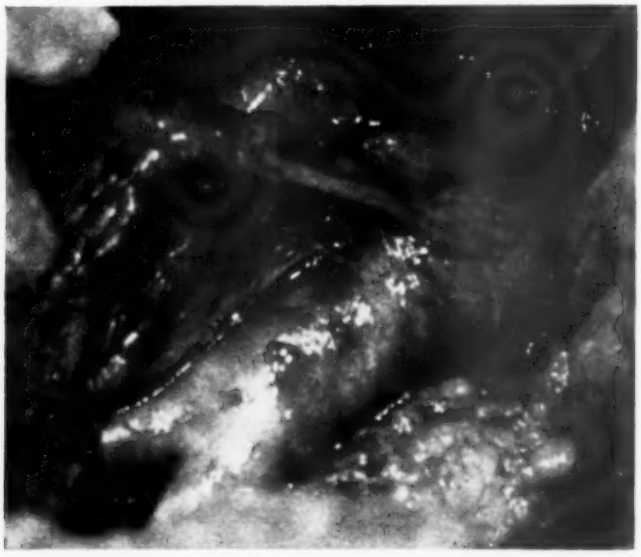

Fig. 2.—Exposure of terminal aorta at level of bifurcation and inferior mesenteric artery.

Fig. 3.—Aorta opened. Thickened intima and thrombus visualized.

The iliac arteries were soft and pliable. The inferior mesenteric artery was soft and contracted (Fig. 2).

Several small lumbar arteries in the thrombosed area were ligated and divided. A larger lumbar artery, in the region of the renal vessels, and the inferior mesenteric artery were occluded with bulldog clamps. After occlusion of the common iliac arteries and the

aorta distal to the renal vessels, a 4 cm. longitudinal incision was made on the left anterior surface of the aorta (Fig. 3). With blunt and sharp dissection, the calcified intima and adherent thrombus were removed (Fig. 4). Several small calcified areas were removed with the curette. Beneath the calcified areas, the entire intima and media were removed, exposing the adventitia. The proximal aortic clamp was released momentarily to flush the upper segment of the aorta. A finger was inserted into the proximal aorta, and no further obstruction or thrombus could be palpated. The incision in the aorta was closed with a running everting suture of No. 00000 silk and re-enforced with a second over-and-over suture of the

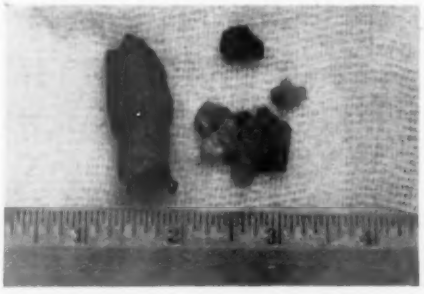

Fig. 4.—Calcified intimal plaque and organized thrombus removed from terminal aorta.

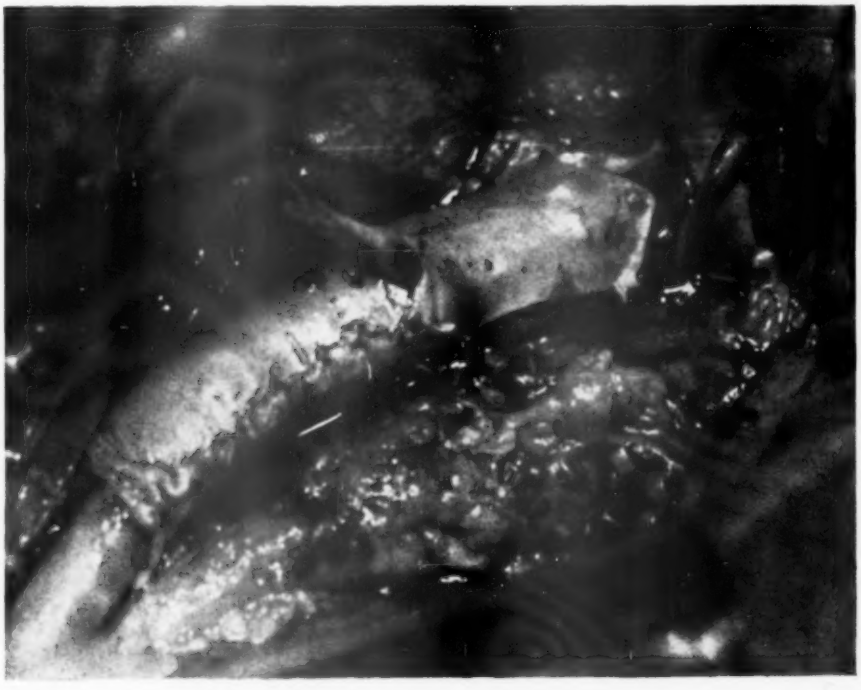

Fig. 5.—Split-thickness skin graft buttress sutured about terminal aorta. Occluding clamps removed.

same material. A split-thickness skin graft was removed from the left side of the abdomen and sutured as a sleeve about the aorta in the region of the dissection. The raw surface of the graft was applied to the adventitia of the aorta. The graft was sutured to fit snugly but not to constrict the vessel (Fig. 5). Upon the removal of the various occluding clamps, there was no evidence of bleeding, and good pulsations were present in both iliac arteries. A bilateral lumbar sympathectomy was performed. At the conclusion of the operation, pulsations were present in the posterior tibial and dorsalis pedis arteries bilaterally.

The patient's postoperative course was uneventful. Heparin solution was instilled into the occluded segment of the aorta as the vessel wall was sutured; however, no anticoagulant drugs were used after operation. At the time of discharge the patient was asymptomatic. He had walked in the country for two and one-half hours without discomfort. All pulses in the lower extremities were normal. The blood pressure in both legs was 112 systolic and 75

Fig. 6.—Retouched postoperative aortogram. Lumen of aorta re-established.

diastolic (mm. Hg), and 115 systolic and 80 diastolic (mm. Hg) in the arms. Oscillometric readings on the lower extremities were:

Position	*Pressure*	*Right Leg*	*Left Leg*
Thigh	140	0.25	0.50
	110	1.50	1.50
	70	1.50	0.50
Calf	140	0.50	0.50
	110	2.50	4.00
	70	4.00	4.00
Ankle	180	0.50	0.25
	110	2.00	2.50
	70	2.00	1.00

The skin of the feet and legs felt warmer than the skin of the hands and arms. The color of the legs, feet, and toes was normal. There was no blanching of the feet on elevation or rubor with dependency. Normal vascular channels in the terminal aorta and iliac arteries were demonstrated by aortography two months after operation (Fig. 6). The patient was returned to duty Nov. 23, 1953.

DISCUSSION

It is generally admitted that the treatment of terminal aortic thrombosis by sympathectomy, with or without aortectomy, is not entirely satisfactory.[2-4]

Removal of the obstruction and re-establishment of the normal vascular channel, the ideal treatment for this condition, have been successfully accomplished by (1) resection of the involved aorta and replacement with a suitable vascular homograft, and (2) thromboendarterectomy. Clinical experience is not sufficient at the present time to establish a clear superiority of either of these two methods.

Further experience may demonstrate specific indications for the utilization of both procedures. In the case presented in this report, the calcified plaque in the aortic wall was localized to a segment less than 2 cm. in length. Removal of the plaque and the proximal thrombus by thromboendarterectomy may prove to be the procedure of choice under such circumstances.

Schafer,[17] in reporting the use of a homologous graft following resection of the abdominal aorta for aneurysm, described a rupture of the wall of the aorta proximal to the graft at the site where calcified plaques had been removed by curettage. Wylie[13] has adequately demonstrated the value of a buttressing material in certain cases following thromboendarterectomy.

The chief advantages of using a skin graft to buttress the weakened aortic wall after thromboendarterectomy are (1) its ready availability, and (2) its tensile strength in all directions.

In 1937, Peer and Paddock,[18] in human experiments, found that sebaceous glands survived for only one week following the subcutaneous transplantation of dermal grafts. Hair follicles survived for a longer period of time. At the end of one year, small cystic cavities were still present, but the epithelial lining was replaced by collagenous fibers. Sweat glands were found in a very degenerated state up to one year. A similar atrophy of the epithelial elements in buried, full-thickness skin grafts in the rabbit has been described by Green and Wollgast.[19] Gray, Mansberger, and Yeager,[20] in their studies of buried, full-thickness skin grafts in experimental animals, were unable to eliminate inclusion cysts, non-union between graft and subcutaneous tissue, and collections of keratolytic debris.

The use of buried, full-thickness skin grafts in the repair of certain types of hernias has been recommended by a number of authors.[21-23]

Sako[24] has studied the use of dermis grafts and split-thickness skin grafts as a buttressing material about autogenous vein grafts inserted in the aorta of dogs. Severe infection, supposedly from pathogenic organisms present in the crypts around the hair shafts and follicles, destroyed the integrity of the graft

in seven of the ten animals in which it was employed. Of four grafted animals treated with penicillin, one died with infection about the graft. Sako stated, "Limited experience with dermis suggests that this . . . is capable of serving as suitable buttress material."

Clinical experience with full-thickness grafts in the repair of hernias suggests that the bacterial flora may be controlled more readily in human skin than in the skin of the dog.

Our patient received 300,000 units of penicillin twice daily for fourteen days. The highest rectal temperature was 101.6° F. on the second postoperative day. The temperature returned to normal on the sixth day after operation. There were no clinical signs to suggest infection about the graft.

SUMMARY

1. A case is presented of thrombotic occlusion of the terminal aorta associated with a localized calcified plaque in the aortic wall.

2. The thrombus and calcified areas were removed by thromboendarterectomy, and the aortic wall was buttressed with a split-thickness skin graft. Satisfactory circulation has been restored to the legs.

3. Thromboendarterectomy may prove to be the procedure of choice in the treatment of thrombotic occlusion of the terminal aorta resulting from localized intimal disease.

4. A split-thickness skin graft is a satisfactory tissue with which to buttress the weakened aortic wall following thromboendarterectomy. It is readily obtained and has adequate tensile strength in all directions.

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A COMPLICATION ARISING FROM THE ATTEMPTED DISSOLUTION OF A COMMON DUCT STONE

Case Report

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NUMEROUS reports in the literature attest to the fact that missed common duct stones can be successfully dissolved in some instances. Further, it is stressed by most authors that no ill effects result from the use of the various solvents. Walker,[1] in 1891, reported the successful use of an ether-glycerin mixture instilled into a biliary fistula which dissolved an impacted stone. Again, in 1908 Wright[2] described a case of impacted duct stones in which the instillation of 1 dram of turpentine was used for dissolution with success. In 1935 Pribram[3] reported on the daily instillation of ether through a catheter with success, and in 1939 and 1947 a total of fifty-one successful cases was reported by the same author.[4, 5]

Ether has been the most widely used solvent for the missed stone, but Walters and Wesson[6] modified Pribram's method, using a two thirds ether and one third ethyl alcohol, followed by warm oil, instillation, with success. Warm chloroform[7] and solution G[8] have also been tried in a few cases for dissolution, with varying success.

The literature is replete with enthusiasm for the method in the occasional cases of the missed stone, and yet there are no reports, to our knowledge, of any complication resulting from the instillation of the various solvents into the common duct or a biliary fistula in man. Probstein and Eckert,[9] after instilling large doses of ether into the gall bladders of dogs, reported clinical jaundice and microscopically progressive destruction of the mucosa with slough, and they concluded that ether may be very toxic when injected into the biliary tract; however, as was so aptly pointed out by Strickler, Muller, Rice, and Baronofsky,[10] they did not follow their injections with oil, the ether was injected into the gall bladder, and the dose, relative to man, was quite large.

We wish now to report on a complication resulting from daily instillation of the ether-alcohol mixture into the common duct over a 21-day period, in which the stone was not dissolved and an ulceration appeared in the common duct which healed without resulting damage to the duct. The stone was later removed surgically, and no damage or narrowing was noted.

CASE REPORT

Mrs. A. K., a white woman, aged 94 years, had been suffering attacks of severe upper abdominal cramping pains recurrently for the previous year. The attacks were becoming so frequent and severe that she had limited her diet to soups, tea, and toast because of fear of pain. She denied back pain, change in color of stools, and dark-colored urine, and had

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never been jaundiced. She had been under the care of her physician, who, on frequent occasions, had felt a right upper quadrant mass that would disappear in a few hours after a hypodermic for pain relief. She was admitted during an attack and, although she was not complaining of severe pain, the mass was palpated on physical examination. X-ray films revealed a nonfunctioning gall bladder. Gastrointestinal x-ray films were normal except for marked diverticulosis of the entire colon. Laboratory findings were all within normal limits, without evidence of subclinical jaundice.

After preoperative preparation with intravenous fluids and vitamin K, operation was performed. A large gall bladder the size of a man's fist was found to be adherent to the duodenum, but was easily freed. It contained one large stone 5 cm. by 3 cm. Palpation of the common duct revealed a stone 3 cm. by 2 cm. situated in the supraduodenal portion of the common duct, and it was easily expressed. A probe passed with ease into the duodenum. The hepatic radicals seemed clear, so a T tube was inserted, and closure of the duct was performed. The patient's postoperative course was complicated only by a feeding problem, and on the tenth postoperative day, a choledochogram (Fig. 1) revealed a negative calculous shadow 1 cm. in diameter in the distal common duct with marked enlargement of the common duct. The duct was not completely occluded because, with clamping of the T tube for twelve- and twenty-four-hour periods, no distress was noted.

Fig. 1.

On the tenth postoperative day, daily instillation of 5 c.c. of Nupercaine Hydrochloride solution for ten minutes, followed by two thirds ethyl-ether and one third alcohol (2 c.c.) instillation was used, and the tube was clamped for ten minutes. Then 5 c.c. of mineral oil was instilled, and the T tube was clamped for one hour. The treatments caused some distress, but the patient tolerated it without difficulty. A choledochogram (Fig. 2) taken in seven days revealed a definite decrease in the density of the stone, but not in the size. A the end of fourteen days, no change was noted in the size of the stone. In twenty-one days (Fig. 3), the stone remained the same. There was a definite ulcer niche noted in the supraduodenal portion of the common duct just above the stone site. Attempts were made to fill the duct completely to obliterate this niche, but it persisted. As a further verification that this was a definite ulceration, four days later the T tube became blocked and, after

repeated irrigations, a bloody mucous plug was expressed. At the end of twenty-eight days (fourth week), after the ether-alcohol treatment had been discontinued and warm saline solution irrigations were being used, the ulcer niche persisted (Fig. 4), but was somewhat improved. At the end of thirty-five days (fifth week), the ulcer niche was present, but improving. Only warm saline solution irrigations were used. At the end of forty-two days

Fig. 2.

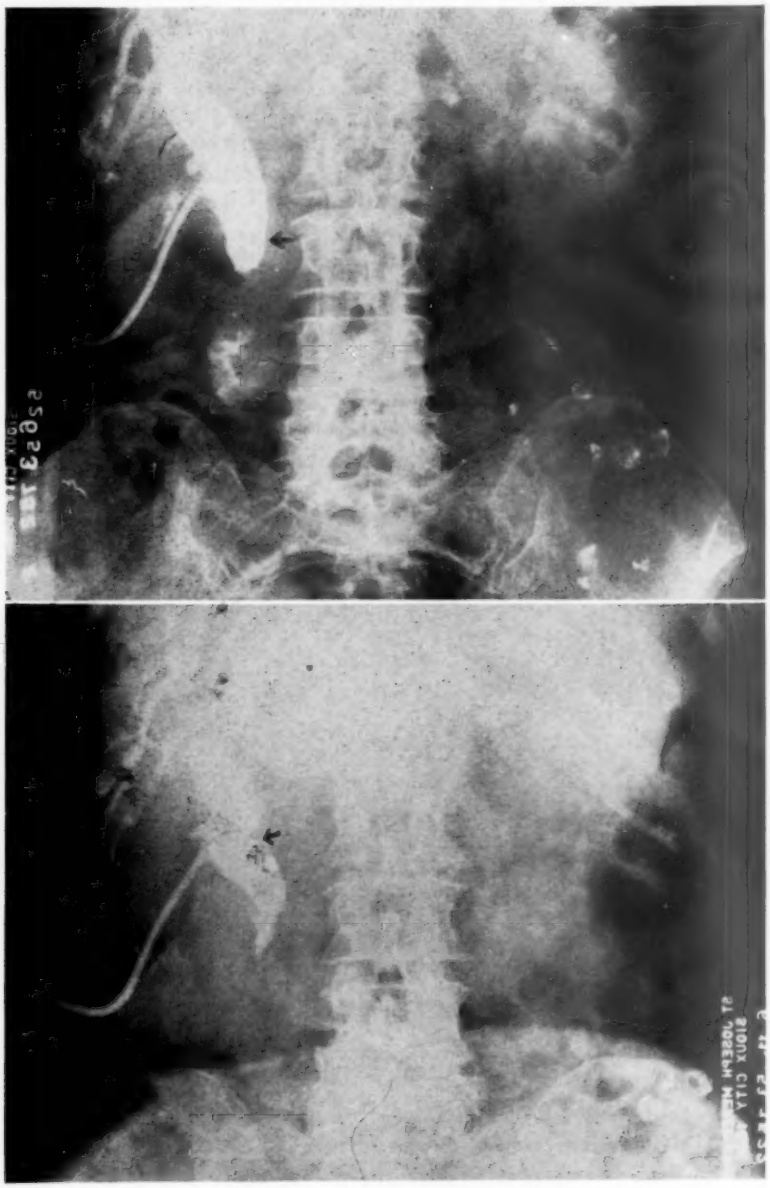

Fig. 3.

(sixth week), the ulceration appeared healed (Fig. 5). There was no residual deformity of the duct; the stone was still present. The patient was re-explored on June 30, 1953, and the common duct stone removed. At this time no narrowing, stricture, or injury to the duct was noted; operative cholangiogram noted the biliary tract to be clear of stones, and a probe

could be passed into the duodenum. A recheck cholangiogram on the tenth postoperative day revealed a normal common duct, slightly dilated, but the dye entered the duodenum without difficulty. There was no evidence of further stones. The tube was removed, and the sinus healed without difficulty.

Fig. 4.

Fig. 5.

CONCLUSION

We feel that this case is of sufficient interest to be presented. Not having seen this complication reported previously, we present this case report, not to condemn the procedure, for we feel it is worth while in selective cases

of poor risks or while waiting for inflammatory processes to subside following the original surgery. We have, on three or four occasions, been successful in dissolving stones; however, we believe if this therapy is tried, one should have weekly choledochograms during the course of the treatment and, if ulceration or irritation is noted, the treatment should be discontinued.

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FIBROMA OF ILEUM (DIAGNOSED PREOPERATIVELY BY BARIUM ENEMA AS BENIGN POLYPOID TUMOR) AND A REVIEW OF BENIGN SMALL INTESTINAL TUMORS

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FIBROMAS of the small intestine are rare, only forty-two cases having been collected by Moore and Schmeisser[1] in 1934. A review of the recent literature brings this number to sixty-six; this count includes the first record of three instances of familial fibromas (really fibromatosis) of the small intestine reported by Hashemian.[2] Our case is the sixty-seventh fibroma and the first benign tumor of the ileum to be detected by barium enema preoperatively or premortem. Fibromas cause intussusception frequently. Many are really mixed tumors such as fibroadenomas, fibromyomas, and fibromyxomas. The positive x-ray findings in small bowel tumors are associated with advanced malignant infiltration or the scout films of intestinal obstruction due to intussusception in benign lesions.

The incidence of small bowel tumors in autopsy material is greater than in surgical material because many are undiagnosed clinically and are found incidentally at autopsy. The location and character of 320 cases of benign tumors (exclusive of pancreatic rests, carcinoids, reduplications, and hematomas) of the small intestine are listed in Table I. These are collected from the data in papers by King,[3] Raiford,[4] Olson, Dockerty, and Gray[5] (which includes thirty-five cases previously reported by Rankin and Newell[6]). Dundon,[7] Weinberger and Paitauf,[8] and Gunkler.[9] The case reports of Lichtenstein and Dutra,[10] Pheils,[11] and our own are included. The data from the remaining publications in the bibliography are also appended.

TABLE I. 320 BENIGN SMALL INTESTINAL TUMORS (EXCLUSIVE OF PANCREATIC RESTS, CARCINOIDS, REDUPLICATIONS, AND HEMATOMAS)

TYPE	DUODENUM	JEJUNUM	ILEUM	NOT SPECIFIED OR ENTIRE SMALL BOWEL	TOTAL
Adenoma	15	9	27	7	58
Chylangioma	—	1	—	—	1
Cystadenoma	1	—	1	—	2
Fibroma	3	10	32	22	67
Hemangioma	8	8	7	32	55
Lipoma	10	8	21	—	39
Lymphangioma	—	4	3	—	7
Myoma, fibromyoma, and leiomyoma	14	24	29	18	85
Neurofibroma	—	1	—	4	5
Osteochondroma	—	—	—	1	1
Total	51	65	120	84	320

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CASE REPORT

Mrs. E. C., history No. 69826, a white woman, aged 62 years, was admitted to Hahnemann Hospital on April 22, 1952, with a chief complaint of periumbilical cramps. She had been in good health until seven weeks before when a sharp pain developed in the left abdomen extending from the costal margin to the level of the umbilicus; this pain lasted eight hours and was relieved by an injection. The pain was unaccompanied by nausea or vomiting. The next day, a similar attack occurred. She was asymptomatic until April 11, when another episode developed; this was described as being sharp and constant and accompanied by distention and was relieved by an injection. She had two loose bowel movements at this time. A barium enema was performed (by M. I.) following subsidence of this third attack. General examination was negative except for moderate obesity, the patient weighing 160 pounds and being sixty-two inches tall. A midline suprapubic healed scar was noted where a ventral suspension of the uterus had been carried out forty years before. The barium enema studies were reviewed in our Department of Radiology. The presence of a polypoid smooth mass (Figs. 1 and 2) in the ileum 45 cm. from the ileocecal valve was confirmed. A preoperative diagnosis was made of benign polypoid tumor of the ileum associated with recurrent intussusception.

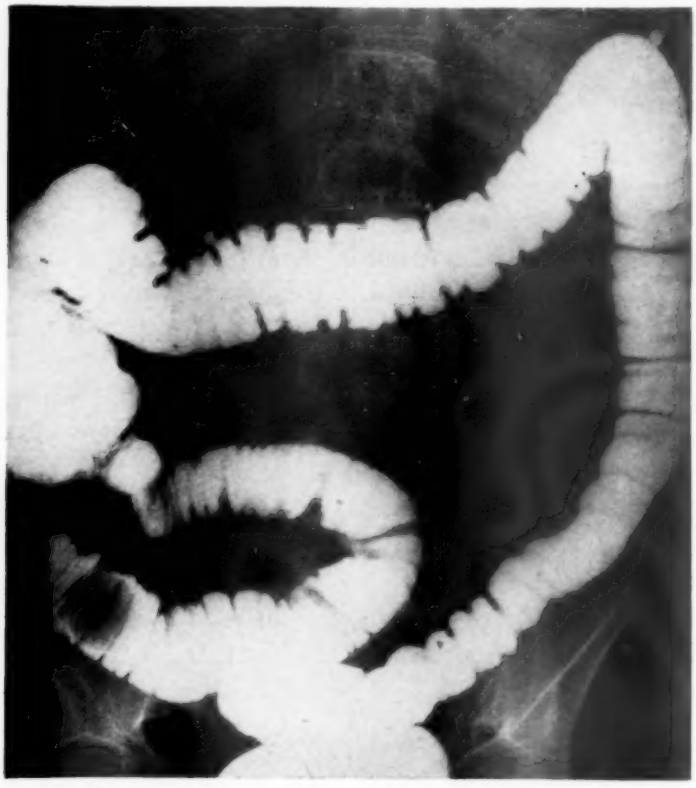

Fig. 1.—Barium enema showing benign polypoid tumor of ileum by reflux.

The patient's intestinal tract was prepared with Sulfathalidine (which had been started before admission) for six days and streptomycin for one day before surgery. On April 24, the abdomen was explored through a right lower quadrant transverse incision (by A. E. P.). A pedunculated, intraluminal fibroma of the terminal ileum, 45 cm. from the ileocecal valve and measuring 3 cm. in its greatest diameter, was found. The terminal ileum was intussuscepted, because of this tumor, for approximately 25 cm. The intussusception was reduced

by gentle taxis, and 25 cm. of ileum with the tumor in the center was then resected and an end-to-end anastomosis performed. The patient's convalescence was uneventful. She was discharged from the hospital on May 2 and has remained well. Pathologic report* revealed a polypoid lesion, measuring 5 cm. in length and 3 cm. in its greatest diameter, attached to the intestinal wall by a stalk which measured 2 cm. in diameter (Fig. 3). The tumor had a smooth surface and was covered by mucous membrane. It was firm in consistency, and on section consisted of homogenous white tissue. Microscopic examination (Fig. 4) revealed it to be made up of a varying texture of loose and dense fibrous connective tissue. The dense areas contained collagenous tissue and many small blood vessels. The looser areas revealed myxomatous degeneration, focal lymphocytes, plasma cells, and eosinophils. The epithelium over the tumor in some areas was hyperplastic and slightly atypical. The final diagnosis was fibroma with degenerative change.

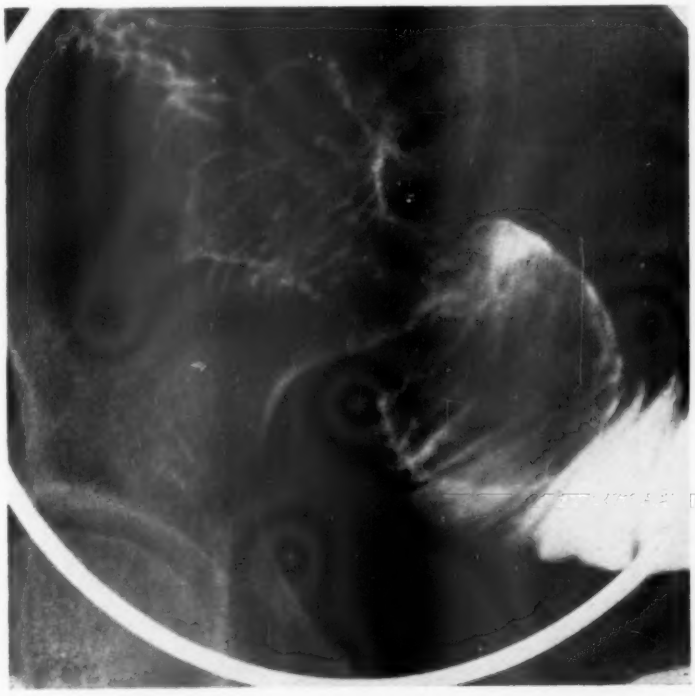

Fig. 2.—Mucosal study of fibroma of ileum.

DISCUSSION

The first comprehensive review of small bowel benign tumors was made by Heurtaux[12] in 1899. King[3] in 1917 and Raiford in 1932[4] and 1933[13] made contributions to this subject.

Raiford found 88 small bowel tumors among 986 gastrointestinal tumors at The Johns Hopkins Hospital in 11,500 autopsies and 45,000 surgical pathologic specimens, many of the latter being samples sent from other hospitals for diagnosis. Of these, 50 were benign (including carcinoids) and 38 were malignant; 4 were fibromas. He found that 37 per cent of the patients produced symptoms warranting surgery. Seventeen per cent had uncertain symptoms and were not operated on, the tumor being found at autopsy. Forty-six per cent

*By Dr. R. Weller.

were asymptomatic and the tumors were found at autopsy. In 1933 Rankin and Newell[6] reported the experience in 35 benign small bowel tumors at the Mayo Clinic. Of these, 18 produced symptoms. Seventeen were found incidentally at laparotomy. In 1935 Kirschbaum[14] reported 12 benign small intestinal tumors in 5,754 autopsies at the Cook County Hospital for the period from 1929 to 1935. In 1939 Merchant[15] summarized the records of the Royal Victoria Hospital of Montreal from 1915 to 1939 and found 6 benign tumors among 50,775 surgical specimens and 18 tumors in 7,340 autopsies. In 1941 Morison[16] reported 11 benign tumors of the small intestine in 13,139 specimens of biopsy and autopsy material. In 1948 Dundon[7] reported the experience at the University Hospitals of Cleveland from 1933 to 1946. Sixty-two small

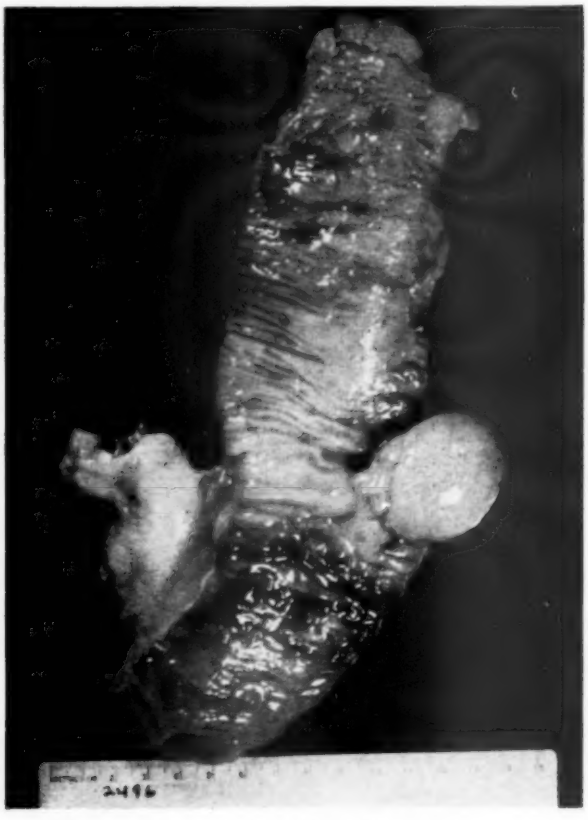

Fig. 3.—Fibroma of ileum.

intestinal tumors were found. Eighteen were malignant and, of these, 13 produced symptoms referable to the gastrointestinal tract or had a palpable mass. The incidence was 1 in 3,000 surgical or 1 in 9,000 general hospital admissions. Of 44 benign tumors, only two produced clinical symptoms. Both of these were pedunculated and caused intussusception. Three benign tumors were incidental findings at operation and 39 benign tumors were incidental autopsy findings. Six of the tumors were pedunculated. In 1948 Weinberger and Paltauf[8] reported 19 records in 20 cases. Of these, 13 were malig-

nant and 6 benign. In their series, 3 benign tumors were subjected to x-ray study; 1 was negative, 1 presented the picture of mechanical obstruction, and 1 produced a filling defect which was diagnosed erroneously as carcinoma of the cecum. All 6 benign tumors were in the ileum. Four of these were fibromas and 1 was a lipoma and the other a leiomyoma. Three were complicated by intussusception. Pheils[11] reported a case of fibroma of the ileum causing intussusception and acute intestinal obstruction; surgery was undertaken after scout films showed small bowel obstruction. In 1951, Olson, Dockerty, and Gray[5] reviewed 77 cases found at the Mayo Clinic. Of these 38 were symptomatic and 39 were found incidentally at operation. Eleven were fibromas. A tumor of the small bowel was suspected in 14 of their cases or 60 per cent of those in which x-ray films were taken. They stated that it was impossible to distinguish various pedunculated tumors from one another. No statement as

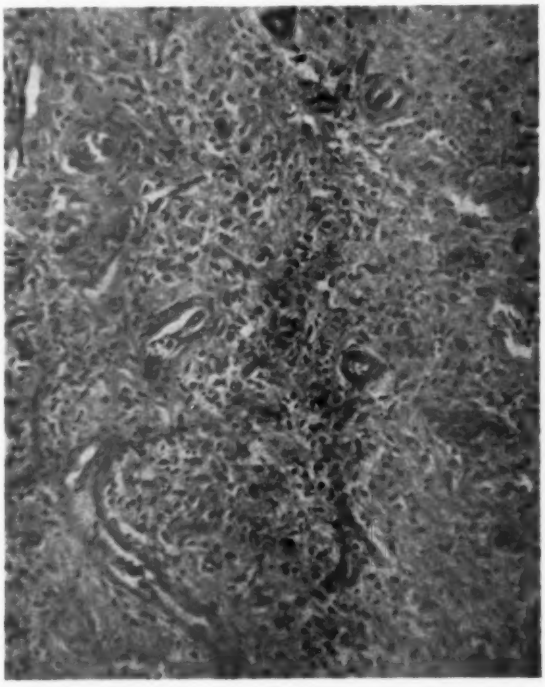

Fig. 4.—Microscopic examination of fibroma of ileum (×80; reduced ¼).

to type of x-ray examination was made. Carman[17] reported the first benign lesion of the small bowel (duodenal hemangioma) found by x-ray examination at the Mayo Clinic. Gunkler[9] collected 138 primary small bowel tumors, including malignancies but exclusive of perivaterian carcinomas, at the Strong Memorial Hospital from 1936 to 1949; 112 cases were incidental autopsy findings and in 26 the tumor was the relevant pathology. In 19 cases, 1 of which was a fibroma, the diagnosis was made before death. Buffard and Crozet[18] reported 7 malignant small bowel lesions and 1 retroperitoneal malignancy. In

addition, they noted 1 large fibroma involving the small intestinal mesentery. Kirkland and Boyer[19] presented a case of multiple lipomas of the duodenum and collected further data on such lesions in this location.

The path of growth of benign intestinal tumors depends on whether the lesion arises on the luminal or on the extraluminal side of the muscular layer. Thus, a submucous lipoma will project into the lumen whereas a subserous fibroma will present toward the peritoneum. Myomatous tumors arising from the muscular layer may protrude in either direction. Extraluminal growths achieve the greatest size because they remain asymptomatic longer. Intraluminal projection of these tumors produces more symptoms. Peristalsis and the downward flow of the intestinal mixture help develop a pedicle. Four complications may occur with a pedunculated tumor of the intestine: (1) bleeding from an eroded surface,[20] (2) intussusception, (3) partial or complete obstruction,[10, 21] and (4) necrosis of the tumor mass.

Tumors of the small intestine should be considered when melena occurs and when study of the esophagogastroduodenal areas and the colon yields negative results. Rather than ascribe gastrointestinal bleeding to a pin-point ulceration or diverticulitis, survey should be made of the small bowel by reflux into the ileum during barium enema and by small intestinal progress films. The diagnosis should also be considered when intussusception is suspected or when small bowel obstruction occurs in an adult who has had no previous intra-abdominal surgery.

SUMMARY

This is a case report of a fibroma of the ileum which produced intussusception and is the first small bowel tumor to be diagnosed by barium enema preoperatively as a benign polypoid lesion. The literature in relationship to benign small bowel tumors has been reviewed.

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ACUTE APPENDICITIS IN AN ADULT WITH TWO SEPARATE VERMIFORM APPENDICES

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THE presence of two separate vermiform appendices, each arising from a separate cecum, is extremely uncommon and was incidentally discovered in a 35-year-old woman operated upon for acute appendicitis. Malformations in other parts of the gastrointestinal tract and in other organ systems included a duplication of the entire colon from the cecum to the lower rectum; a double terminal ileum; a Meckel's diverticulum; a complete absence of the right kidney with a corresponding hypertrophy of the left kidney; and, finally, a bicornuate uterus. These rare and unusual findings in an adult female, previously asymptomatic and who had delivered two healthy children, were considered worthy of a detailed report.

CASE REPORT

The patient, M. R. (523431 A), a 35-year-old white housewife, was seen for the first time in the Emergency Room at the University Hospital on the evening of May 12, 1952, with the *chief complaint* of abdominal pain of some twenty-four hours' duration. The patient had been completely well until just after retiring on the previous day. At that time she noted an increasing discomfort in the upper abdomen, which gradually developed into colicky pain. These symptoms were followed by nausea, and early on the day of admission a single episode of spontaneous vomiting had occurred. The cramplike pains became constant and were located in the right lower abdomen at the time of examination. The patient recalled no similar episodes in the past. Menstrual periods had been regular and the last one occurred seven days previously. There were no urinary symptoms and no history of chills and fever, diarrhea, or change of bowel habits.

The *past history* was of interest in that some type of surgery for an imperforate anus had been performed soon after birth. This operation had been carried out in Spain, and no details of the procedure could be obtained. Other operative procedures included a tonsillectomy in 1928, and a vaginal repair following normal childbirth in 1943. Because of the previous perineal repair, a cesarean section was performed in 1948, but the patient related no knowledge of an abnormal uterus being present. There had been no miscarriages. She was happily married and had two normal living children.

Physical examination showed a well-nourished, normally developed woman with obvious abdominal pain. Temperature was 100.6° F., pulse 100, respirations 20, and blood pressure 120/80. The heart and lungs were normal. There was definite localized tenderness in the right lower quadrant which was associated with muscle spasm and rebound tenderness in the right lower abdomen. Abdominal distention was absent, and no masses were palpable. Peristalsis was active and normal. Pelvic and rectal examination increased the lower right-sided abdominal pain, and movement of the cervix was not painful. The *laboratory data* included a white blood cell count of 18,900 with 87 per cent neutrophils. The red blood cell count was 4,300,000 and the hemoglobin was 12.2 Gm. Complete examination of a catheterized urine specimen was negative. A diagnosis of acute appendicitis was made and the patient was prepared for surgery.

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Findings at Operation.—To avoid a second abdominal scar, the peritoneal cavity was entered through the old right paramedian cesarean incision, and on opening the peritoneum a small amount of free straw-colored fluid was encountered. An apparently normal cecum was identified and presented a normal-looking appendix, approximately 4 cm. in length, which had been lying along the right lumbar gutter. It was at once apparent that further exploration was necessary to account for the patient's symptoms and laboratory findings. As the cecum was delivered to permit identification of the terminal ileum, an additional and more medially located cecum with a separate appendix was seen. This second appendix measured 5.5 cm. in length and was tense and obviously acutely inflamed (Fig. 1). Its surface was covered with a suppurative exudate, and its middle portion showed a bulbous enlargement that measured 2.5 cm. in diameter.

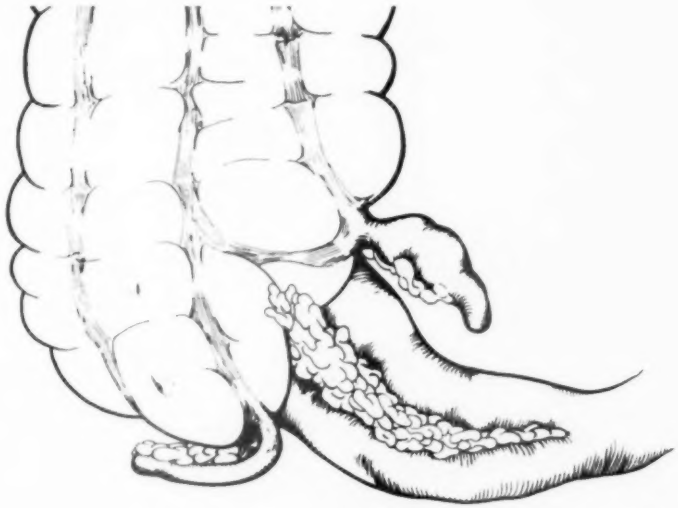

Fig. 1.—Diagrammatic sketch illustrating, in a 35-year-old patient, M. R. (No. 523431 A), two separate vermiform appendices, a double terminal ileum, and a double cecum. The laterally placed appendix was normal and the second, more medial, was acutely inflamed. The double cecum, with its three taeniae, seemed continuous with the remaining colon, which is not shown here, but was proved to be duplicated to the lower rectum. No abnormal dilatation of the bowel was present at any point.

As determined by a sterile metal ruler, the distance between the bases of the appendices measured 8 cm. The appendiceal artery of the inflamed appendix seemingly originated from a thickening on the medial side of the mesenteric leaf of the terminal ileum. The blood supply of the normal appendix seemed to arise from the opposite side of this same mesentery. The ceca resembled the limbs of an inverted Y, with its base a common ascending colon. The lateral cecum was funnel shaped and appeared not unlike that seen in the dog. The large bowel proximal to the obvious duplication presented three separate taeniae; the central taenia divided into an inverted Y, with its limbs proceeding toward the base of their respective appendices. These limbs approximated 7 cm. in length. The remaining taenia also terminated in a similar fashion, but without division.

The distal 12 cm. of terminal ileum also presented a duplication, which seemed to be complete. Each of the segments was of normal size and separated by a fatty mesentery up to the ileocecal junctions, where they terminated at the base of the inverted Y-like cecum between the appendices. The lateral, or inferior, ileum measured 1.5 cm. in width, and the medial, or more superior, 2.5 cm. Both appendices were removed and, following phenol cautery, the stumps were inverted with a purse-string silk suture.

Additional exploration of the terminal ileum resulted in the finding of a noninflamed Meckel's diverticulum about 3 cm. in length and located 35 cm. proximal to the ceca. This diverticulum was removed at its base, transverse to the long axis of the bowel, and the defect was repaired with two tiers of interrupted inverting silk sutures. The species removed at the time of operation are shown in Fig. 2.

A normal-sized uterus was fund lying in the left side of the pelvis with a single normal tube and ovary attached. An accessory and smaller uterine-like structure was attached to its right side at about the level of the internal cervical os. An additional normal-appearing tube and ovary were identified emptying into this structure. These findings were interpreted as representing a bicornuate type of uterus. The right kidney could not be identified and the left was estimated to be from one and one-half to two times normal size. The urinary bladder was not remarkable. The liver felt normal, and a single gall bladder without stones could be palpated.

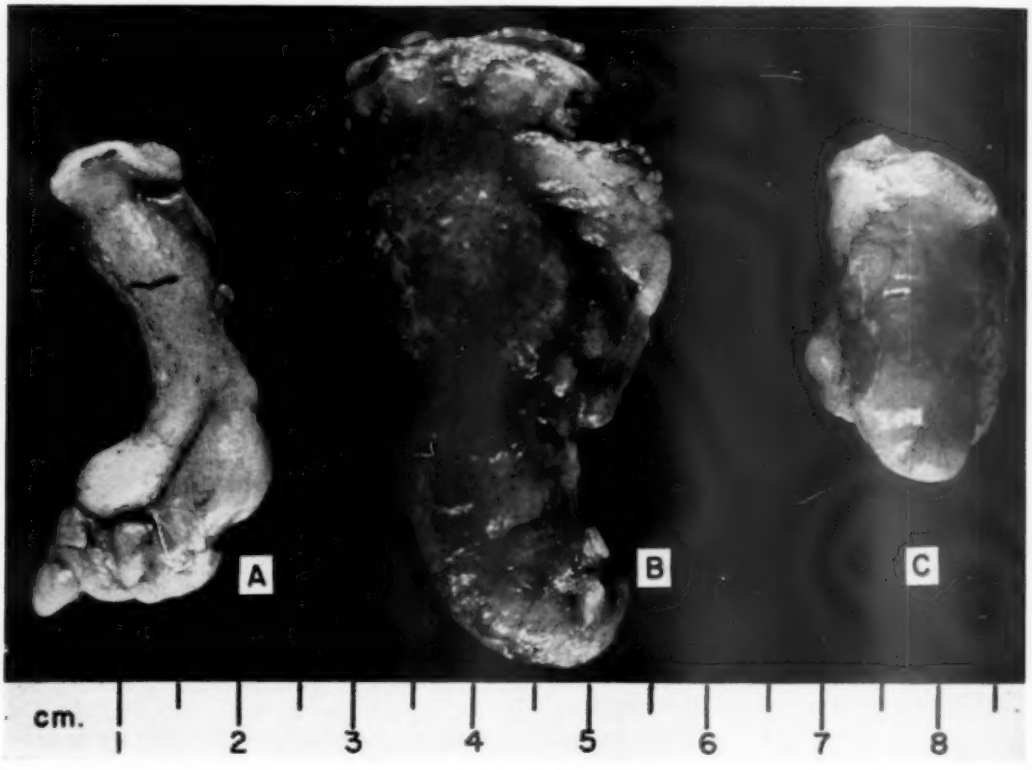

Fig. 2.—The specimens removed at operation included (*A*) normal appendix; (*B*) an acutely inflamed appendix; and (*C*) a noninflamed Meckel's diverticulum.

The postoperative convalescence progressed without incident. The *microscopic diagnosis* included (a) normal vermiform appendix; (b) acute suppurative appendicitis; and (c) Meckel's diverticulum with a thin muscular wall which was lined with small bowel mucosa, but which showed no evidence of inflammation. After we discussed the presence and significance of these congenital abnormalities with both the patient and her family, she was released from hospital care on the seventh postoperative day. Arrangements were made at that time to have the patient return for x-ray confirmation of the remaining congenital anomalies of the gastrointestinal and genitourinary tracts that were found at the time of operation.

On *roentgenologic study,* three weeks after discharge, an upper gastrointestinal series demonstrated a normal esophagus and stomach, with a normal emptying pattern. The segments of small intestine visualized during this examination showed no abnormality, and no reduplication could be identified. A detailed study of the small bowel was not obtained. Fluoroscopy of the large intestine proved to be of great interest (Fig. 3, *A*). The barium filled the rectum easily without evidence of obstruction, and immediately thereafter split into two separate columns which persisted through the descending, the trans-

verse, and the ascending colons. The duplicated sigmoid was directed forward and into the right lower quadrant, where it turned sharply to the left and proceeded in an upward direction to the splenic flexure. At this point, they doubled back and descended again to the right lower quadrant, where two ceca were observed. Neither segment of the duplicated terminal ileum was filled at this examination. The reduplication of the colon was again demonstrated by an air contrast study (Fig. 3, *B*).

The shadow of the left kidney was easily identified on a plain kidney, ureter, and bladder film, and an excretory urogram showed good visualization of the same kidney (Fig. 3 *C*). These studies failed to visualize the right kidney. The functioning kidney, which showed fetal lobulations, was unusually large, and measured approximately 15 by 7.5 cm. Its pelvis was not dilated and its calyces retained their normal cupping. Dye was identified in the urinary bladder, but no abnormality was demonstrated. X-ray examination of the chest was not remarkable.

DISCUSSION

Duplication of the appendix is a comparatively rare anomaly and, unless associated with other grave abnormalities, is entirely compatible with a normal existence. The degree of duplicity of the appendix varies from a partial duplication to the presence of two distinct appendices arising from a double cecum. Menten and Denny[6] reported a collective series of thirty-eight cases of duplications of the vermiform appendix in which the possible embryologic derivation of the anomalous appendices was also discussed. Five of the thirty-eight patients had a partial duplication of the appendix, that is, conjoined with two separate lumens. Thirty-three were found to have completely separate appendices, twenty-five of these arising from a single cecum, and in the remaining eight, each appendix originated from a separate cecum.

The majority of duplications of the alimentary tract are found occurring in conjunction with other congenital anomalies.[5] The case herein described was associated with a complete duplication of the colon from the cecum to the lower rectum and, in addition, a double terminal ileum was also present. The fact that this particular type of congenital anomaly, in itself, is also quite rare is shown by Ravitch[7,8] in his recently reported surveys of twenty cases of hind-gut duplications. Three-fourths of these patients had a complete duplication of the colon, and five had an associated double terminal ileum. One case included a triplication of the entire colon.[3] A single mesentery and a single blood supply were noted in most instances. The majority of these reported cases were associated with some type of genitourinary abnormality, which fact is of extreme importance to the welfare of the patient since many could be corrected if discovered early. Approximately one-half had an associated double appendix, and many of these were included in the reports by Greig[4] and by Menten and Denny.[6] Only one case[9] of the entire series occurred in an adult, and to the best of our knowledge, there has been no instance in which a complete duplication of the colon has been reported in an adult with no previous symptoms.

A diagnosis of duplication of the small or large intestine is usually made in infants or young children, and to find any such anomaly in an adult is extremely rare.[1, 2, 5] This is true since the duplication generally ends blindly or connects with a small inadequate fistula which results in operation for

Fig. 3.—(*A*), Roentgenograms of the colon after introduction of a contrast enema. The denser shadow probably represents the more normal colon. Note the common rectum and the absence of any abnormal distention of the bowel. The course of both colons is readily seen; note the empty left gutter. The terminal ileum is not visualized. (*B*), Postevacuation of the roentgenograms of the colon demonstrating, again, the duplication of the entire colon. (*C*), Excretory urograms showing good visualization and enlargement of the left kidney without dilatation of the renal pelvis, the calyces retaining their normal cupping. The right kidney was not visualized.

symptoms related to an ulcerative process or to intermittent or incomplete intestinal obstruction. When duplication is present, early operation is usually necessary with either excision of the duplication, in the case of small intestine, or in the case of large bowel, anastomosis of the blind pouch to the normal sigmoid or rectum.

This particular patient was unusual, inasmuch as she had survived to adulthood without symptoms from the hind-gut duplication. Had it not been for the attack of acute appendicitis, these congenital anomalies might have persisted indefinitely. The findings at operation and subsequently by x-ray examination indicated a duplication of the entire colon from the cecum to the rectum, with a common communication of each colon to the lower rectum, which terminated in a single anal orifice. The drainage afforded by this common communication, together with the almost normal-sized junction between the double ceca and the duplicated terminal ileum, apparently allowed sufficient passage of ileal contents to account for the normal existence of the patient to adulthood without symptoms.

SUMMARY

A case is reported in an adult woman, aged 35 years, with the two separate vermiform appendices, each arising from a separate cecum. This anomaly was discovered at the time the patient was operated upon for acute appendicitis and was found to be associated with a complete duplication of the colon and the terminal ileum. Except for symptoms of acute appendicitis, the patient, at no time previously, had any symptoms referrable to the hind-gut duplication. An analysis of previously reported cases, as well as from our limited experience, suggests that a patient with a duplication of the hind-gut, whether an infant or an adult, should have a complete investigation of the gastrointestinal tract and, of more importance, the genitourinary system in order to avoid the overlooking of associated anomalies that might be corrected.

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HOMOLOGOUS AND AUTOGENOUS SKIN GRAFTS IN A CASE OF HEMOPHILIA

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THIS paper is presented with a twofold purpose: first, to report what is believed to be one of the first homologous skin grafts employed in a case of hemophilia; and, second, to investigate the length of survival of a homologous skin graft in this condition and to compare this length of survival with that in the case of a nonhemophiliac person. Autogenous skin grafts have been successfully carried out previously in this condition.[1]

CASE SUMMARY

J. B., a 32-year-old white man, known to be hemophiliac, was admitted to University Hospital on Aug. 7, 1953. Two months prior to admission, the patient had bruised the left thigh accidentally. A day or two later he noted a marked swelling and redness over the lateral aspect of the thigh. This area became increasingly painful, and several days later the skin began to blister. Shortly thereafter the skin began to break down and drain serosanguineous fluid. The thigh then became infected, and he was admitted to a hospital, where he was given penicillin. The draining area became larger, and it began to bleed more severely. He was given 6 units of blood during this admission. The infection subsided, and the patient was sent home. He continued to have serosanguineous drainage of the wound.

After five weeks' bed rest at home, the patient was readmitted to the same hospital because of weakness and was given three more transfusions. Following this, he was transferred to the Hematology Service at the Ohio State University Hospital. Upon admission to this hospital, the patient appeared to have a severe chronic anemia. There was diffuse swelling of both knees from previous episodes of hemorrhage into the joints. There was diffuse enlargement and subcutaneous swelling over the lateral aspect of the left thigh, with deep bronzing of the overlying skin. There were several openings, roughly 4 cm. in diameter, in the skin in this area. At the depths of these, there was necrotic granulation tissue and a moderate amount of serosanguineous fluid (Fig. 1).

Past History.—The patient was known to be hemophiliac and had had repeated episodes of hemorrhage into the joints, especially the knees. He had bruised easily all his life and had had many large subcutaneous hematomas.

Family History.—This patient had three living brothers, all of whom had hemophilia. One brother died at the age of 12 years as a result of hemorrhage following an accident. The father was not hemophiliac. There was no history of blood dyscrasia on either the paternal or maternal sides of the family.

Laboratory Data.—On admission, red blood count was 2,000,000; hemoglobin was 6.3 Gm. per cent; platelet count was 1,000,000; white blood count was 4,750, of which 72 per cent were neutrophils, 2 per cent eosinophils, 22 per cent lymphocytes, 4 per cent monocytes; hematocrit was 24. Coagulation time was thirty minutes by the Lee-White method. Prothrombin time was 52 per cent of normal. Culture of the wound was reported as *Escherichia coli, Aerobacter aerogenes,* and beta Streptococcus. All organisms were sensitive to penicillin, chloromycetin, Aureomycin, and Terramycin.

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Hospital Course.—This patient was given frozen plasma and fresh whole blood immediately upon admission and daily thereafter, in order to restore his blood volume and to give the necessary antihemophiliac factors. The patient was first seen by the Surgical Service two days after admission. It was felt that the evacuation of the infected hematoma was indicated as soon as the hemophilia was controlled. Penicillin, streptomycin, vitamin K, and vitamin C were also given. His coagulation time decreased until it was fifteen minutes by the Lee-White method.

Fig. 1.—Thigh showing massive hematoma.

Fig. 2.—Granulating wound showing incision and drainage.

On Aug. 12, 1953, five days after admission, the lateral aspect of the left thigh was incised. A huge, infected, foul-smelling blood clot was evacuated. It was estimated that this blood clot represented 1,000 to 1,500 c.c. of blood. A pressure dressing was applied, and the patient was started on Terramycin, since cultures reported organisms sensitive to this drug. Vitamin C, vitamin K, and transfusions of fresh whole blood and frozen plasma were resumed. Five days after operation the patient began to bleed slowly. The following day he was taken to surgery and a dressing of the wound was done. A large granulating wound covering the major part of the lateral aspect of the thigh was present. Pressure dressings were reapplied. The patient's course from that time was one of repeated wound dressings at five-day intervals. These were necessitated by slow bleeding. Throughout this period, his coagulation time varied from one hour to normal by the Lee-White method. However, the episodes of bleeding seemed to have no relation to the length of coagulation time. Throughout the period of dressings, the patient's wound remained quite clean and gradually began to decrease in size, until it measured about fourteen by six inches (Fig. 2).

The problem then arose as to the best way to cover this wound. Secondary closure would have been possible only with excessive undermining. This was thought inadvisable because of the fact that at previous wound dressings it was noted that hematomas had

dissected extensively along the fascial planes. The other possibility was a split-thickness skin graft applied to the granulating wound. We were hesitant to take skin from the patient for fear of further bleeding and possible breakdown of the donor area. It was

Fig. 3.

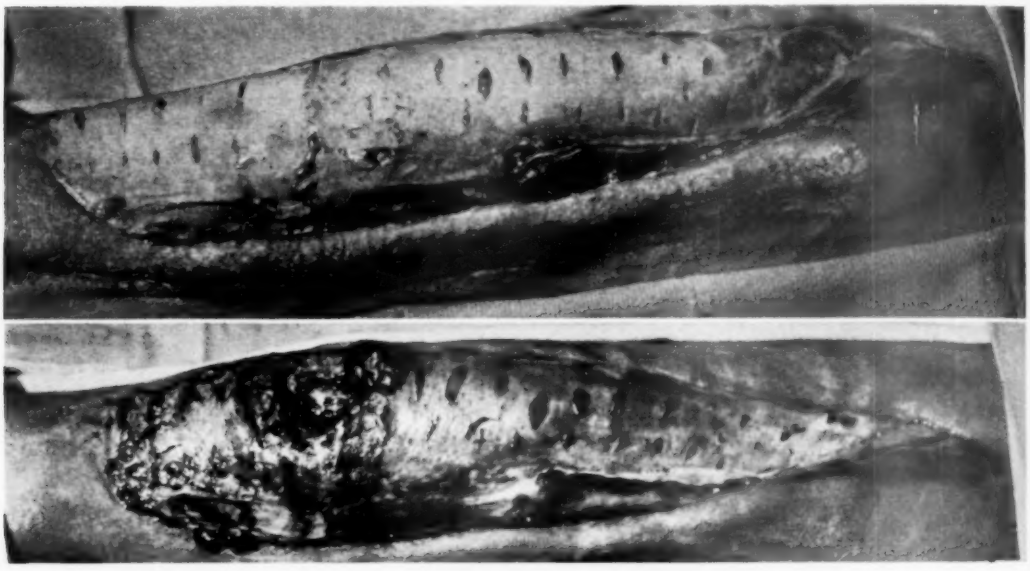


Fig. 4.

Fig. 3.—Homologous graft at ten days.
Fig. 4.—Homologous graft at seventeen days.

Fig. 5.

Fig. 6.

Fig. 5.—Homologous graft at twenty-two days.
Fig. 6.—Autogenous skin graft shortly before patient's discharge from the hospital. There are a few crusts present. These were not dislodged because of fear of bleeding.

therefore elected to use a homologous skin graft for the following reasons: It was thought that even though the homologous skin graft would be only temporary coverage, it would allow shrinkage of the size of the wound so that less of the patient's own skin would be needed at a later date to cover the defect. We were also interested in studying the possible effects of hemophilia on the survival of a homologous skin graft, since clotting in capillary loops is presumably a factor in the failure of these grafts generally.[2]

Three strips of skin were taken from the thighs of a fresh cadaver with a Brown dermatome at 0.015 of an inch. These grafts were placed in a refrigerator at 40° F., and twelve hours later the skin was placed on the patient's granulating wound without suturing. Pressure dressings were then applied. In five days, when the first dressing was done, there was 100 per cent "take" of the homologous graft. A biopsy was taken at this time, and subsequent dressings and biopsies were made on the tenth, twelfth, seventeenth, twenty-second, and thirtieth days. After thirty days, there was complete absence of any of the homologous skin graft. The wound had decreased about 50 per cent in size. This resulted from scar tissue contracture rather than any appreciable ingrowth of epithelium. It was felt that the homologous graft had greatly reduced the fluid and blood loss. However, because of the potential threat of bleeding, it was necessary to maintain transfusions of whole blood and plasma.

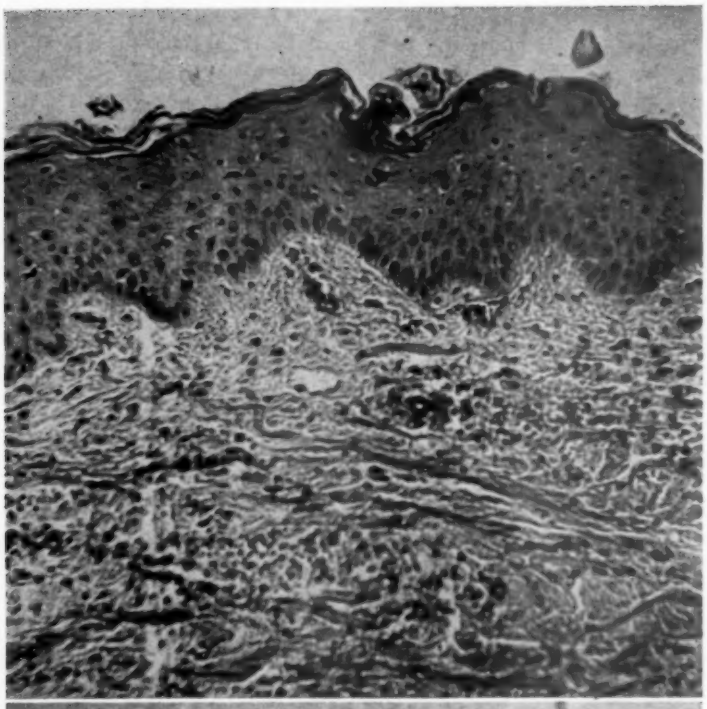
At this time an autogenous skin graft was taken at 0.008 of an inch thickness with a Reese dermatome from the same thigh and applied to the clean granulating wound. The preoperative regime was resumed. Following surgery, the patient was given fresh whole blood and frozen plasma each day for five days. On the fifth day the wound was dressed and there was complete "take" of the autogenous split-thickness graft. The defect was closed and remained so until the patient's discharge from the hospital. (Fig. 6.)

Throughout the patient's entire postoperative course, his caloric intake was high. His total protein and albumin-globulin ratio remained normal. He received a total of 47 units of blood and 35 units (250 c.c. each) of frozen plasma. Twenty-six anesthetics were administered. These were Pentothal, and were of short duration.

DISCUSSION

As has been previously stated, the homologous graft was used with a twofold purpose in mind. First, to provide a temporary skin covering for a large granulating wound, thus allowing the size of the wound to shrink so it would require less of the patient's skin to cover it when autogenous skin grafting was done; also, to prevent as much as possible loss of fluid and blood. Second, we were interested in studying the possible effects of hemophilia upon the survival of homologous skin grafts. Discussions of the theory of failure of homologous skin grafts have been thoroughly presented elsewhere.[3-6] The most generally accepted theory to date is that proposed by Medawar.[7-12] He postulated that dissolution of the homologous graft is caused by an immune response on the part of the recipient to genetically different tissue of the same species. Skin homografts between monozygotic, or identical, twins is successful, since genetically identical tissue is employed. Conway and co-workers,[2] using transparent tissue chambers as modified by Joslin, have observed frequent thromboses in the capillaries of the recipient bed in mice and felt that this may be the manifestation of the immune response by the hosts. Attempts to alter this immune reaction by physical, chemical, immunologic, and hormonal means have been generally unsuccessful. The problem of human skin homografting thus remains unsolved.

Fig. 7.



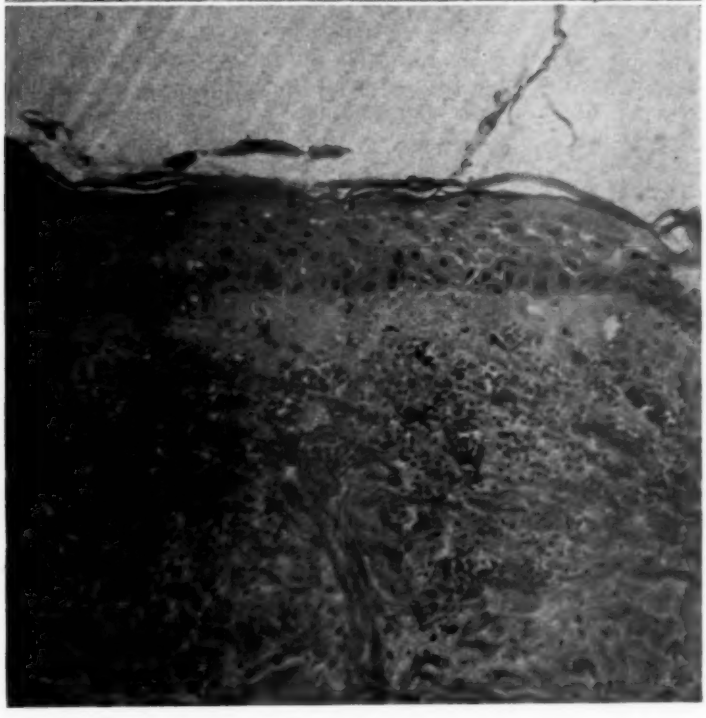
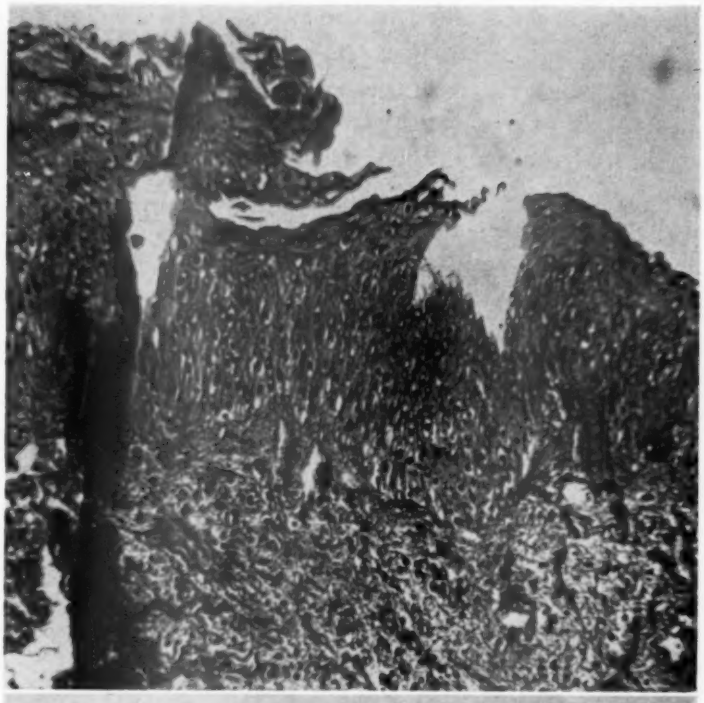


Fig. 8.

Fig. 7.—Photomicrograph of biopsy of homologous graft five days postoperatively.

Fig. 8.—Biopsy, ten days postoperatively. Shows considerable round cell infiltration and desquamation. There is capillary invasion.

Fig. 9.



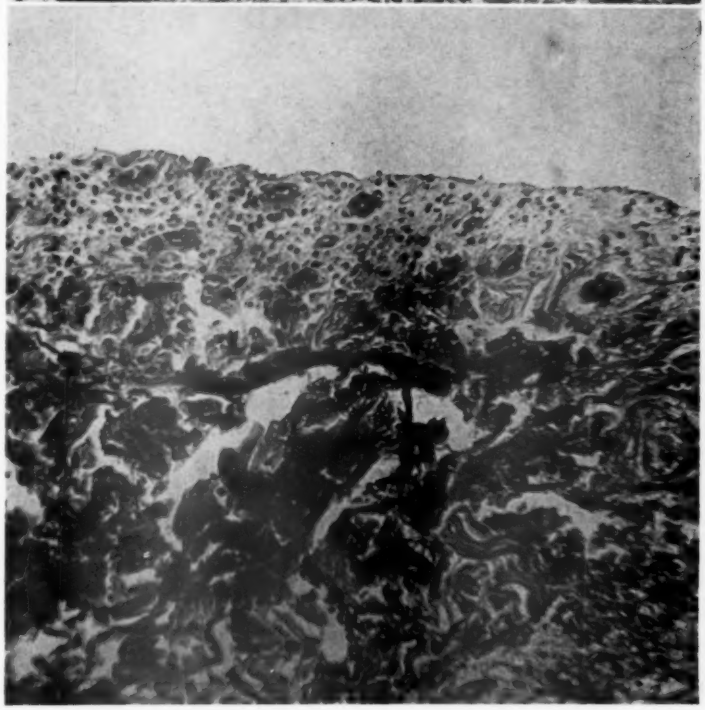


Fig. 10.

Fig. 9.—Biopsy, twelve days. Desquamation and infiltration more marked. Capillary infiltration is quite prominent.

Fig. 10.—Seventeen days. Complete loss of epithelium. More round cell infiltration, occasional giant cells, and remnants of elastic and collagen fibers.

In the case presented, the homologous skin graft was taken from a cadaver two hours after death and applied to the recipient twelve hours later. It was stored in a refrigerator at 40° F. during the interim. When the graft was dressed initially at five days, there was complete "take" grossly and microscopically. Biopsies taken on the tenth, twelfth, seventeenth, twenty-second, and thirtieth days showed the usual changes present in the dissolution of a homologous skin graft in a nonhemophiliac person. At first, a viable graft with beginning capillary vascularization was present. At ten days there was superficial desquamation with round cell infiltration in the underlying dermis. At seventeen days there was complete loss of the epithelium. At no stage did

Fig. 11.—Twenty-two days. Complete dissolution of the graft, similar to that seen in a normal individual.

thrombosis of the capillaries appear to be an important factor. At the seventeenth day there were still remnants of collagen and elastic fibers of the homologous graft with rapid invasion of these structures by capillary loop and a rather marked infiltration of round cells and large mononuclear cells. In some areas in the biopsies, giant cells could be seen. At the twenty-second day the picture was quite similar to that which has been described previously in a nonhemophiliac person. The biopsies at thirty days showed complete absence of any elements of the homologous graft. The presence of previous homologous grafts did not seem to alter the "take" of the autogenous graft, which was subsequently applied with complete success.

CONCLUSIONS

There is no definite difference in the survival of a homologous skin graft in a person with hemophilia as compared to that in a person without hemophilia, both histologically and chronologically. The presence of the previous homologous skin graft did not alter the success of a subsequently applied autogenous skin graft.

The homologous graft was of great value in preservation of body fluids and blood, and in the reduction of the size of the wound, so that a much smaller amount of the patient's own skin was required for final closure.

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HEMANGIOPERICYTOMA (GLOMUS TUMOR) OF THE MEDIASTINUM

Review of the Literature and Report of Case

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THE NORMAL GLOMUS

THE neuromyoarterial glomus was first described by Masson in 1924.[1] He found that the normal glomus is a neurovascular structure which is located at the junction of the skin and subcutaneous tissue. It is present in much greater numbers in the hands and feet than in other regions of the human body, and is composed of an afferent arteriole, anastomotic vessels (canals of Sucquet-Hoyer), collecting veins, nonmedullated nerve fibers, and a supporting network of reticular connective tissue. The walls of the anastomotic vessels are unusual in that they are surrounded by several layers of rounded cells which are epithelioid in appearance but are apparently contractile in function. The glomus, as a whole, is a tiny arteriovenous anastomosis which supposedly assists in the regulation of skin temperature by increasing or decreasing the amount of blood flowing through the canals of Sucquet-Hoyer. It may also have some slight function in the regulation of the arterial blood pressure by changing the peripheral resistance to blood flow.

THE GLOMUS TUMOR

Histology.—Masson also related the glomus to tumor formation, and stated that the glomus tumor is composed of a mixture of all the tissue elements which compose the normal glomus. It was his belief, then, that the glomus tumor is a hamartoma of the normal glomus. However, he realized that within each tumor, a single type of cell seemed to predominate, and he classified glomus tumors into the angiomatous, epithelioid, and neuromatous varieties.

Since Masson's original description, pathologists have not been in exact agreement concerning the tissue details necessary for the microscopic diagnosis of glomus tumor. There is, of course, agreement that blood vessels and epithelioid cells must be present, but not all observers are sure that the presence of nerve fibers is necessary. Weidman and Wise[2] reported a case in which there were forty-eight lesions that were typical glomus tumors from the histologic viewpoint except for the absence of nerve fibers. They stated that, to them, the distinctive feature of the glomus tumor is the Sucquet-Hoyer canal. Slepyan,[3] on the other hand, presented a case of a patient who

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had fourteen glomus tumors, in which nerve elements were found in abundance. Lemmer[4] also emphasized the presence of nonmyelinated nerve fibers seen between the glomus cells. Mason and Weil,[5] in an extensive review of the literature, found that there is not agreement as to the significance of nerve fibers and their endings, and cited other authors' opinions that the nerve elements are not an integral part of the tumor. Kay and associates[6] stated that nerve fibers are often missing from glomus tumors which occur at sites away from the hands and feet.

Clinical Characteristics.—In general, most reported glomus tumors have been found in regions of the body where normal glomera occur in the largest number, namely, the immediate subcutaneous region of the extremities. The typical glomus tumor is described as a small, purplish red nodule which is very painful to touch, pressure, and sometimes even to movement of the extremity. Although pain is usually a prominent symptom, it is not necessarily present. Weidman and Wise's[2] patient with forty-eight lesions had no pain (and no nerve fibers within the tumors); Slepyan's[3] patient with fourteen identical tumors, all containing nerve fibers, had pain in only two of them.

From the previously mentioned reports of multiple glomus tumors, it might seem that multiplicity is common. Such is not the case. The growths are far more often single. They are usually encapsulated, easily removed, and benign. Murray and Stout[7] found reports of only two malignant glomus tumors; they questioned their authenticity, but were able to add the report of another case in which the tumor recurred locally twice and necessitated the amputation of a foot.

Heterotopy of Glomus Tumors.—Although most reported glomus tumors have been found in the subcutaneous region of the extremities, many other locations have been noted. Examples are the subcutaneous region of the eyelid, penis, axilla, thorax, buttocks, neck, and coccyx, the vastus internus muscle, and the capsule of the knee joint.

More heterotopic tumors have been found in the stomach, three cases having been reported by Kay and associates.[6] Heretofore, only a single case of a mediastinal glomus tumor has been reported.

Heterotopy of glomus tumors was not well understood until the appearance of a report in 1942 by Murray and Stout.[7] They found that the epithelioid cells which form a contractile cuff around the walls of the anastomotic vessels are identical with pericytes of Zimmerman, or contractile cells of the capillaries. By the method of tissue culture, they learned that the rounded "epithelioid" cells actually have small bodies with many cytoplasmic processes, but that their physical characteristics are obscured when they are crowded into a cuff around a small blood vessel.

HEMANGIOPERICYTOMAS

Definition.—With Murray and Stout's discovery, it became apparent that tumors combining small blood vessels and pericytes might occur at any point in the body, and might or might not be associated with nerve fibers. Such

neoplasms could have the microscopic characteristics of a glomus tumor and yet might not be an actual hamartoma of a previously existing neuromyoarterial glomus.

In 1942, Stout and Murray[8] reviewed the microscopic sections of their collection of blood vascular tumors and found thirty-eight glomus tumors. In addition, they found that there were nine instances in which the neoplasm in question was not, in their opinion, a glomus tumor, yet was composed of capillary blood vessels with one or more layers of rounded cells about their walls. According to their terminology, these atypical tumors lacked the "organoid" microscopic appearance of the typical glomus tumor. They suggested that the descriptive term "hemangiopericytoma" be applied to such neoplasms.

Histology.—In 1949, Stout[9] reported a study of twenty-five additional cases of hemangiopericytoma, contributed by sixteen different pathologists. From his study of these tumors, he concluded that the possible variation in the gross and microscopic appearance of the growths is endless, but that in all instances, there is a profuse proliferation of either obvious or "occult" capillaries (endothelial buds either with or without a lumen), each capillary or endothelial bud being surrounded by a connective-tissue sheath. Outside the sheath, he found the pericytes, which may vary greatly in appearance, depending upon their number and the degree of crowding or compression within the tumor.

Distribution.—Distribution of the reported hemangiopericytomas within the body has been wide. In addition to the subcutaneous region, Stout[9] has found the tumors to occur in the lower part of the neck, in the tissues of the arm, on the dorsum of the tongue, between the kidney and adrenal gland, in the mesentery of the jejunum, in the anterior leaflet of the pericardium (anterior parietal pericardium), in the orbit, in the popliteal region, in the left pleural space with origin from the left leaf of the diaphragm, in the retroperitoneal region, and in the lower part of the ileum. Others have reported the tumors to occur in the thigh,[5, 10] in the sigmoidal mesentery,[11] in the axilla,[12] as a mass filling the true pelvis,[12] and in the extrarectal region.[13]

Clinical Behavior.—Until the present time, we have been able to discover forty reported cases of hemangiopericytoma. The clinical behavior of these tumors has been unpredictable. It seems that about one-third of them exhibited malignant characteristics, as metastasis occurred in seven of the forty cases, and at least seven other tumors exhibited an aggressive, invasive type of growth without metastasis. The remainder were apparently benign.

Pathology.—There are no characteristic features in the gross appearance of the tumors. A red color is not necessary, nor are gross characteristics suggestive that the growth is a vascular one. The consistency of the reported lesions has varied from soft and cystic to hard and "fibrosclerotic." A capsule may or may not be present and may be incomplete. Although most of the reported tumors are small, they may attain great size, filling one-half

of the pleural space or all of the true pelvis. They may occur at any age; in three of Stout's reported cases the tumors were congenital, and in the others they were in patients whose ages were spread through the decades of life, the oldest patient being 81 years of age.

The single distinguishing characteristic of hemangiopericytoma is its microscopic appearance, and even that may vary within a wide range. Certainly, some hemangiopericytomas are very similar to glomus tumors. In one sentence of their original article, Murray and Stout[7] actually stated that the term "hemangiopericytoma" might be applied to glomus tumors. From subsequent reports, it seems that they have kept the glomus tumors and hemangiopericytomas separate. Whether or not the separation has been kept complete is, to us at least, open to question, as in 1951, Kay and co-workers[6] reported the previously mentioned glomus tumors which occurred in the stomach; none of these tumors contained nerve fibers. It would seem to us that, according to Stout's own terminology, these tumors might well be hemangiopericytomas with the appearance of glomus tumors.

INTRATHORACIC GLOMUS TUMORS AND HEMANGIOPERICYTOMAS

With the previously stated ideas in mind, we should like to review the medical literature concerning the glomus tumors and hemangiopericytomas which have occurred within the thorax, and to add the report of a case seen by us.

Review of Literature.—The first and only reported case of a "glomus tumor" occurring within the thoracic cavity was that by Brindley in 1949.[14] The tumor occurred in a white woman, 29 years of age. It had produced symptoms of pain in the right lower part of the thorax for a period of nine years. The pain was always present, of inconstant severity, with intermittent paroxysms being present. The paroxysms were induced by movement, coughing, and deep breathing. The patient stated that two years previously, a rounded, purple, tender tumor had been removed from the left groin, and that subsequently, several other tumors had appeared on the right lower extremity. Physical examination revealed four purplish, tender tumors on the right lower extremity, and a roentgenogram of the thorax disclosed the presence of an area of increased density, a mass, in the posterior mediastinum. All of the tumors were removed, and all were found to be glomus tumors. Microscopically, they were identical, composed of vascular spaces surrounded by cuboidal epithelioid cells, and containing numerous nonmedullated nerves. The mediastinal tumor reported in this case seems to us to be a typical glomus tumor, and microscopic sections of the tumor were examined by one of our colleagues. We cannot explain its origin as a hamartoma or hyperplasia of a normally occurring, pre-existing glomus.

In the latest reported study by Stout,[9] he described two hemangiopericytomas which occurred within the thorax. One was a disklike plaque, 5 by 5 by 0.5 cm. in dimensions, occurring in the anterior leaflet of the peri-

cardium of an elderly woman. The other was a large, vascular, brown-red tumor which filled one-half of the left pleural space of a woman, 23 years of age. It seemed to arise from the left leaf of the diaphragm.

CASE REPORT

The case which we wish to present is that of a white girl, aged 16 years, who was first seen at the Mayo Clinic on July 17, 1953, for evaluation and treatment of a tumor within the thoracic cavity. The tumor had been first noted in February, 1953, when a roentgenogram of the thorax had been taken during the course of a routine physical examination. To the patient's knowledge, the growth had produced no signs of its presence. A review of her systemic symptoms, however, revealed that for four years, she had noted drooping of the right eyelid, especially when she was fatigued. Her past medical history was noncontributory. Review of a roentgenogram of the thorax taken in 1947 revealed nothing pathologic, but re-examination of one taken in 1952 disclosed that the lesion was present at that time.

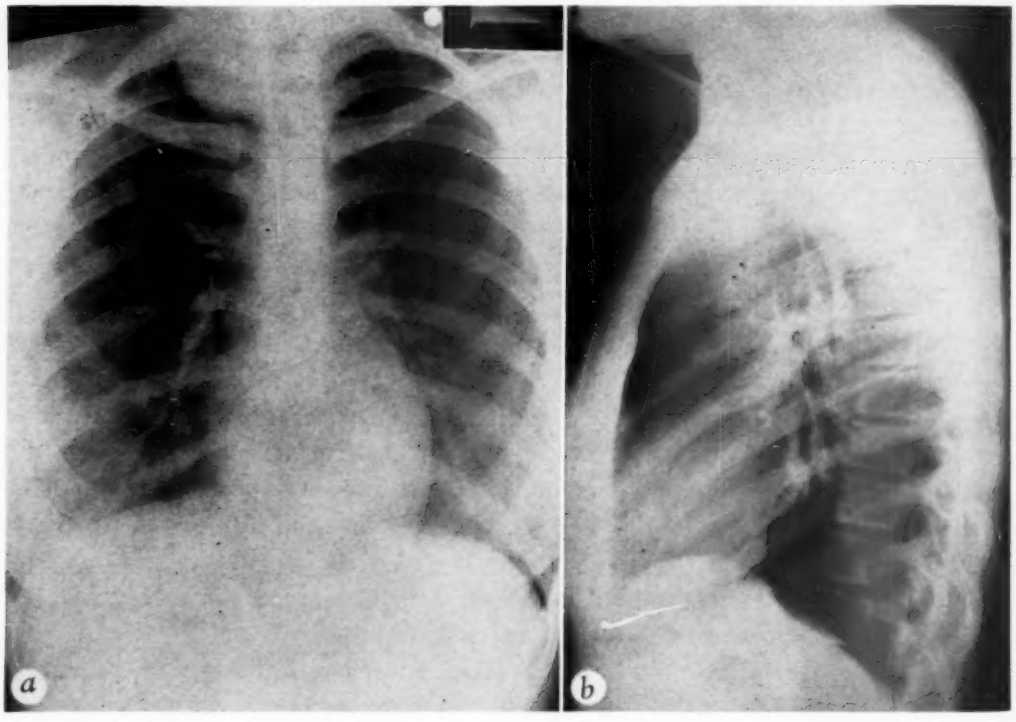

Fig. 1.—*a* and *b*, Tumor is shown at the apex of the right thoracic cavity (hematoxylin and eosin; ×130).

Physical examination showed the patient to be well developed and nourished. The blood pressure was 114 mm. Hg systolic and 64 diastolic. The right pupil was miotic, and the right upper eyelid was slightly lower than the left. Pupillary reflexes were normal. The thorax, heart, and lungs seemed to be perfectly normal. There were no other masses present in any other region of the body.

The results of laboratory examination of the patient's blood and urine were within normal limits. The value for hemoglobin was 12.6 Gm. per 100 c.c. of blood; the erythrocyte count was 4,140,000 cells and the leukocyte count 5,600 cells per cubic millimeter. Serologic test for syphilis gave negative results. The erythrocyte sedimentation rate was 12 mm. in one hour. Roentgenographic examination of the thorax revealed the presence of a well-circumscribed soft-tissue mass in the apex of the right thoracic cavity, with possible slight extension of the mass into the neck (Fig. 1).

Taking into consideration the location of the tumor, the duration of its presence, and the Horner syndrome produced by it, the most logical preoperative diagnosis seemed to us to be that the neoplasm was either a ganglioneuroma or neurofibroma, with involvement of the right sympathetic trunk. Surgical removal was advised, and the operation was performed by one of us (O. T. C.) on July 21, 1953. A small posterior vertical incision was made on the right, between the vertebral border of the scapula and the spinous processes of the upper dorsal vertebrae. A segment of the posterior portion of the second right rib was removed, and the mass was exposed.

As removal of the tumor was begun, severe bleeding was encountered, and it became evident that the tumor was not the ganglioneuroma or neurofibroma expected. The incision was extended. A long segment of the second and a smaller segment of the first rib were excised in order that the tumor might be well visualized. It was seen that the blood supply of the tumor was very rich, with blood vessels entering it from its entire surface. The tumor was dissected from its bed with great difficulty and considerable loss of blood. It was particularly adherent to the apex of the thorax and to the first rib, and there may have been a small extension of it into the neck. Severe bleeding prevented the clean dissection desired. An absorbable gelatin sponge (Gelfoam) was placed in the bed of the tumor in order to control oozing from the thoracic wall. A 30 Fr. red rubber catheter was inserted into the right pleural space for the purpose of temporary closed intercostal drainage. Aqueous penicillin, 240,000 units, was instilled through the catheter, and the thoracic wall was closed in layers around it. During the operation, the patient received 1,000 c.c. of whole blood by transfusion.

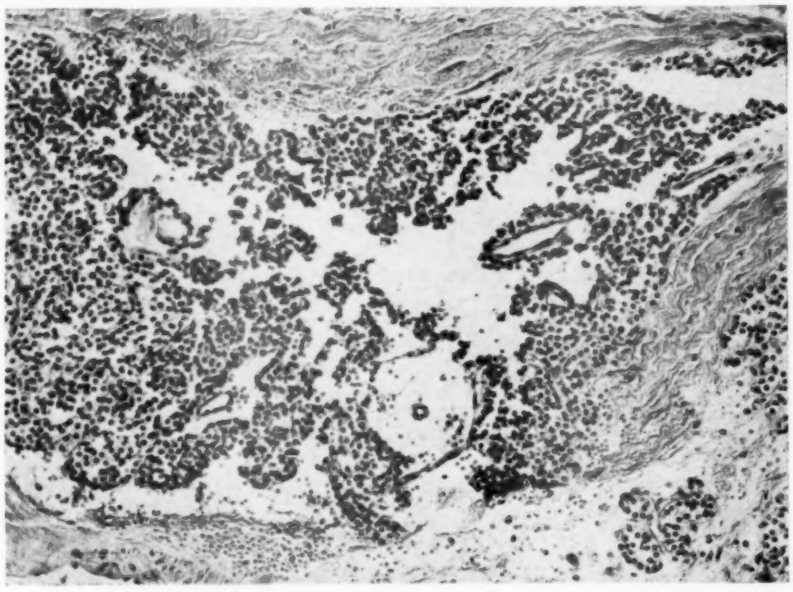

Fig. 2.—Section from the tumor shown in Fig. 1. See text for details.

The patient's postoperative course was entirely uneventful. The catheter was removed from the thorax in twenty-four hours, and the patient left the hospital on the seventh postoperative day. Dermal sutures were removed on the ninth postoperative day, and the patient was dismissed from our care at that time. A recent letter from her referring physician states that she now is feeling well, is participating in all the usual physical activities, and that the Horner syndrome has improved.

Examination of the excised tumor by one of us (J. R. McD.) revealed it to be a solid, red, meaty-appearing growth, containing a considerable amount of blood. It was

encapsulated, but the capsule was incomplete. It measured 5 by 3.4 by 1.5 cm. Microscopic sections were stained with hematoxylin and eosin. Blocks of the tissue were also stained for the presence of nerve tissue, according to the Bodian technique. Examination of the sections revealed that the tumor was extremely vascular and that it was composed of rounded cells with regular, sharply demarcated nuclei (Fig. 2). The tumor cells formed collars around the vessels. The vessels had an endothelial lining, but no smooth muscle in their walls. Mitotic figures were not seen. There was no nerve tissue in the tumor.

SUMMARY AND CONCLUSION

We believe that the case we have reported represents the second glomus, or glomuslike, tumor and the third hemangiopericytoma occurring within the thoracic cavity to appear in the medical literature. The tumor occurred at the apex of the right thoracic cavity in a girl 16 years of age, and produced Horner's syndrome on the right. Surgical removal was very difficult and possibly incomplete because of the extreme vascularity of the tumor, its anatomic location, and incomplete encapsulation. The patient's postoperative recovery seems complete, and the Horner syndrome is said to have improved.

The marked similarity between the typical glomus tumor and at least some of the hemangiopericytomas has been stressed. We feel that in all likelihood, most of the glomus tumors reported as occurring in regions of the body distant from the subcutaneous tissue are probably hemangiopericytomas which are indistinguishable from hamartomas of pre-existing glomera.

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Editorial

Duodenal Ulcer: Its Surgical Treatment

THE confusion concerning peptic ulcer, a general disease with a local lesion, might be diminished by subdivision into:

1. Gastric (separated because of malignant potentialities). (Esophageal and jejunal are omitted because of comparative infrequency.)
2. Duodenal: (a) uncomplicated and (b) complicated.

The following remarks will refer to treatment of complicated duodenal ulcer, that is, by correction of the complication (perforation, hemorrhage, or organic obstruction) and attempts to prevent recurrence of the ulcer.

Operative treatment has been a gradual development:

From indirect (after secretion) neutralization of gastric contents by alkaline duodenal regurgitation after pyloroplasty or gastrojejunostomy;

To presently accepted distal partial gastrectomy which adds direct (before secretion) removal of more and more HCl secreting parietal cells of the proximal stomach, in a so-called "shift to the left"[1] and removal of the alkaline-secreting antrum with its alleged hormonal stimulant to HCl secretion, so-called Edkins' "gastrin" (probably histamine or an H-like substance).

The remote results have not been entirely satisfactory because of:

A. Insufficient removal of parietal cells.

B. Loss of the antrum with its protective alkaline mucous secretion, reservior, and mixing function. (Loss of gastrin is of questionable value because of its continued postoperative secretion by Brunner's glands, and elsewhere.[2]

C. Loss of pyloric sphincter mechanism with resultant abnormal gastrointestinal continuity, too early gastric emptying, and unregulated duodenal regurgitation. (Postoperative attempts of nature at a stomal sphincter action have been demonstrated at x-ray examination.)

The stomach is essential for temporary food storage and mixing with digestive secretion in preparation of its controlled entrance into the duodenum, all of which are seriously interefered with by the presently accepted distal gastrectomy.

Continued stimulation of the parietal cells of the remaining proximal stomach by psychic influences, nervous "tension," or emotional conflicts is a disadvantage that led Dragstedt to vagotomy.

In the surgical treatment of duodenal ulcer, it is necessary to realize that the human stomach is a double organ: (a) proximal (fundus and body) containing parietal (hydrochloric acid-secreting) cells and (b) distal (antrum and

pylorus) with alkaline mucus-secreting cells and the regulatory sphincter mechanism.

The clinical significance of this evolutionary, embryologic, anatomic, and physiologic fact becomes apparent when one realizes that removal of the hydrochloric acid-secreting parietal cells (found chiefly in the proximal stomach) fulfills the accepted objective of treatment, the reduction of gastric acidity by direct removal of the secreting apparatus itself. This would also nullify the influence of the various stimuli (neural, humoral, hormonal, mechanical, endocrine, or others) because there will be few or no parietal cells to be stimulated.

Such an operation, proximal partial gastrectomy[3] treats chronic hyperchlorhydria similarly to the successful partial thyroidectomy in treatment of hyperthyroidism, and results in the following favorable details:

1. Removal of the hydrochloric acid-secreting parietal cells.
2. Retention of alkaline-secreting antrum: retention of Castle's intrinsic factor.
3. Retention of sphincter-regulating mechanism with modified reservoir and mixing function.
4. Retention of normal gastrointestinal continuity.

The fact that it required two decades to prove that gastroenterostomy was not a cure for peptic ulcer[4] (in 1932 gastroenterostomy in 75 per cent and in 1951 in 10 per cent reported by Mayo Clinic) emphasizes the necessity of longer "follow-ups" in evaluating results.

It also directs attention to the possibility of early favorable results being, perhaps, due to the gastroenterostomy and not to the coincidental surgical procedure.

In the customary description of 50 to 75 per cent of gastric resection, the percentage might better be applied to the percentage of proximal parietal cells instead of to the whole stomach. This emphasizes the advisability of identifying partial gastrectmoy as either distal or proximal.

My clinical experience[5] in twenty-five cases of "partial fundusectomy," with five unsatisfactory results, plainly indicates the necessity of removal of more proximal stomach.

Wangensteen,[6] Nagel,[7] MacLean,[8] and others,[9, 10] have discussed this procedure with case reports.

—F. Gregory Connell

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

IMMEDIATE RECONSTRUCTION OF THE INJURED HAND

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IT IS often true that "time is the friend of the surgeon." In the management of the injured hand, any loss of time may be of great importance. An unwise delay in treatment may work against the surgeon in such a manner as to prevent him from obtaining an otherwise good result.

The hand is peculiar in this regard because of its great intricacy of closely moving parts. Without movement, the hand loses most of its functional value. Reconstruction is successful only if effective motion of the thumb and fingers is regained.

Sensation is also highly developed in the hand, the surface of which constitutes our "touch pad" with the physical world. Yet, because of the many sensory fibers present, the injured hand is often painful. Consequently, movement of such a hand is greatly reduced, and the evils of immobilization soon follow.

As plastic techniques have developed, they have been used to answer some of these difficult challenges of hand repair. While many traumatized hands still require multiple operations and weeks or months of exercise and splinting, certain injuries demand prompt action.

SKIN LOSS

Loss of skin is common in burns, avulsions, wringer injuries, or finger amputations. In the past, the burned hand has been simply dressed and the slough has been allowed to develop, demarcate, and separate. Braithwaite[1] has pointed out that during this period "the skin by its generalized contraction, interferes with the vascular supply of the hand and renders ischemic many tissues primarily unharmed by the burn." A period of three weeks might pass before grafting is possible. Another two or three weeks of immobilization is required for healing of the graft.[11] This month and one-half of immobilization is always accompanied by pernicious stiffening of the delicate joints of the fingers. The collateral ligaments shorten, and fine fibrous adhesions anchor tendons and joints.[2] Such joints never regain full motion. Expensive hospitalization is prolonged, and the patient suffers increased pain and morbidity.

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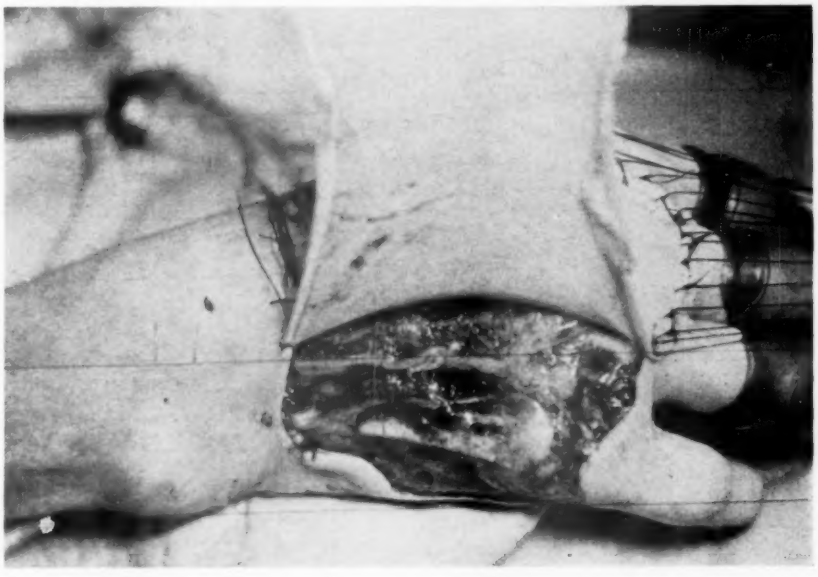
We have found that, in the burned hand, a complete loss of sensation to pinprick means third degree loss of skin. This will determine, with reasonable accuracy, the area of slough to be expected. Once the extent of third degree burn could be established, several of these hands were grafted within a few hours of arrival at the hospital. If course, all such patients should be in good general condition, and the burns elsewhere on the body should not be so extensive as to endanger life. With the aid of a careful skin preparation, and a blood pressure cuff tourniquet for hemostasis, the anesthetic skin is dissected away, taking care to include a small margin of overlap into the surrounding blistered skin. It is best to have the graft slightly larger than necessary. The depth of excision should leave the tendon sheaths intact if a split

Fig. 1.—This hand was burned only three hours before operation. Blisters have been trimmed and areas of second degree burn are seen on wrist and thumb. Skin of dorsum of palm and fingers was pale and completely anesthetic to pinprick. Edema may be seen in underlying subcutaneous tissue, but split graft took perfectly. This hand regained full function within five weeks of burn, while the left hand, burned less severely, was not grafted for fourteen days after burning and was still quite stiff in metacarpophalangeal and interphalangeal joints over four months later, when patient was last seen.

graft is to be used. It has been quite easy to determine if the deep tissues are destroyed by gross inspection. We were, at first, fearful that the grafts might not "take" on beds containing acute traumatic edema. This has not been the case, and all grafts have healed per primam (Fig. 1). They are dressed in place with pressure bandages, and the hand is splinted in the "position of function." These hands begin active exercise within one week after the burn, and obtain almost complete motion before the conventional treatment would allow a slough to form and separate. If the graft edges are properly shaped, to avoid late, straight-line contractures, no further surgery

is needed. Even if only the right hand is grafted, as in the case of patients with other major burns, such patients are able to feed and care for themselves in the subsequent course of their treatment (Fig. 2, *A* and *B*). The eyelids, if burned, are also grafted early in order to preserve the cornea. Cultures of the

A.

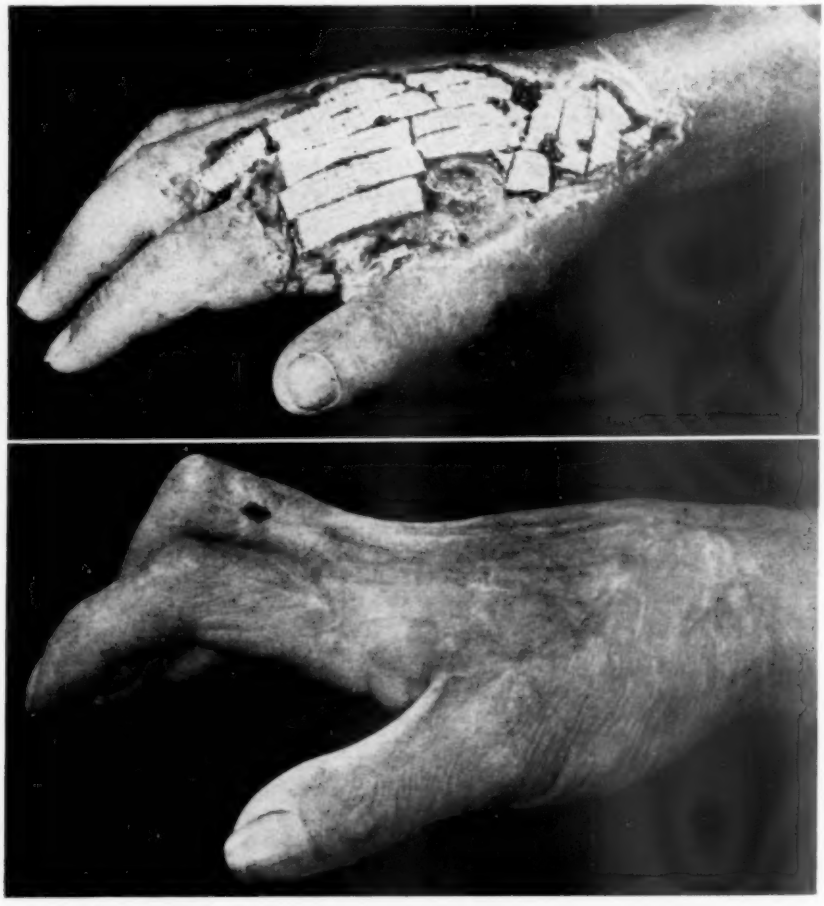


B.

Fig. 2.—*A* and *B*, This hand was deeply burned by contact with an electric coil during sleep. Immediate grafting with a split graft on the transparent tendon sheaths resulted in full "take" and excellent hand function within three weeks.

surface organisms from third degree burns show a marked increase in the number and variety of bacteria about ninety-six hours following injury. After this period, it is probably wise to consider the burn an infected surface, and to defer grafting.

A.



B.

Fig. 3.—*A*, This burned hand was allowed to "granulate" and the stamp grafts were applied eighteen days after burning. Healing occurred in two additional weeks.

B, Same hand seven years later shows hyperextension deformity of metacarpophalangeal joints due to contracture of fibrous tissue in original granulating bed. Hand is virtually useless. Late repair now requires arthroplasties and tendon replacement, necesitating a pedicle flap for skin coverage at the time of deep work. Immediate split grafting and early splinting would have avoided these drastic measures and given superior hand function.

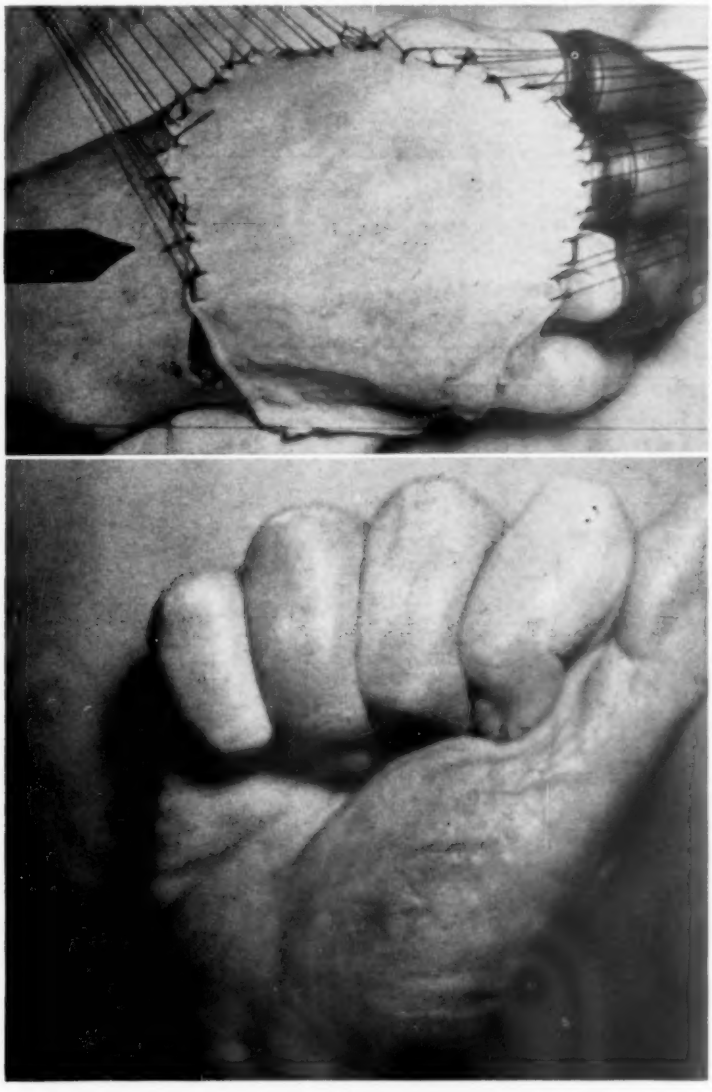
Hyperextension deformity of the metacarpophalangeal joints tends to develop, to some degree, in all major burns of the dorsum of the hand. Splinting and careful exercise will not prevent this. To allow slough, granulation tissue, and infection to appear is to allow fibrosis and stiffening (Fig. 3, *A* and *B*). Immediate grafting will cut short this process and leave mobile the critical metacarpophalangeal joints. If granulating beds are allowed to develop, grafts should never be placed simply on top of these. In such cases the con-

Fig. 4.—Combined arthodesis of damaged metacarpophalangeal joints and application of undelayed flap to traumatic injury of hand. A plaster cast would have been impossible to apply in such a case and Kirschner wire fixation is most helpful to gain bone fixation.

Fig. 5, *A*.—Wringer injury in 65-year-old lady. Obvious impending of skin and exposure of tendons.

tracture will then occur beneath the skin as the fibrocytes form and collagen is deposited. It is quite feasible to carry out arthrodesis of any interphalangeal joints at the same time that the split grafts are applied. We prefer Kirschner wire fixation for this, and reserve the procedure for instances in which the

B.



C.

Fig. 5, *B* and *C*.—*B*, Immediate split graft of hand in Fig. 5, *A* after excising flap back to bleeding dermis.

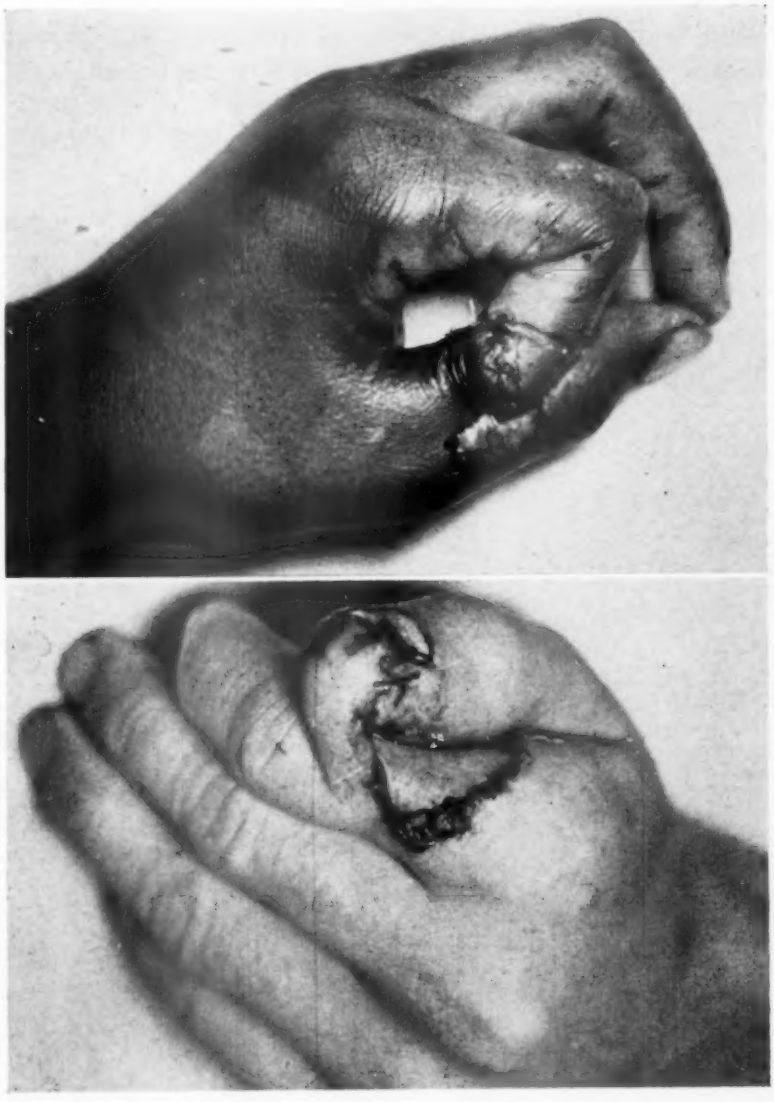
C, In spite of edema, graft "took" 100 per cent, and patient had this range of flexion in four weeks.

tendons are badly burned or the cartilaginous joint surfaces are scarred or fractured (Fig. 4).

The same principles may be applied to wringer injuries or avulsions in which the deep structures are largely intact. If a slough is allowed to develop

slowly, over a wringer hand, an astonishing mass of fibrous tissue forms about the tendons on the dorsum, and hand stiffening may be irreversible, epecially in the aged[10] (Fig. 5, *A*, *B*, and *C*).

A.



B.

Fig. 6.—*A* and *B*, Simple methods of supplying bone coverage for tips of thumb and index fingers. These are outpatient procedures, and the flaps can usually be divided in twelve to fourteen days.

Avulsions of flexor surface of the hand may require a better working surface than is furnished by split-thickness skin. Here is the principal need for immediate reconstruction is the importance of covering and, thus, preserving exposed bone or tendon that has been denuded of its fascia.[7] The cross-digital, palmar, and cross-arm flaps[5, 9] do yeoman service in such circumstances (Fig. 6, *A* and *B*).

The importance of preserving bone length in the distal phalanx has been largely overlooked until recently. Split grafts will not grow on projecting stumps of bone, and the surgeon's only alternative to flap repair is to shorten the already shortened phalanx even further, in order to close the finger tip. This usually reduces the length of the distal phalanx sufficiently to eliminate its usefulness as a flexing surface. Requests to have finger length restored, after such needless amputations, are ample evidence of the importance of these finger tips to the patient (Fig. 7, *A*, *B*, *C*, and *D*).

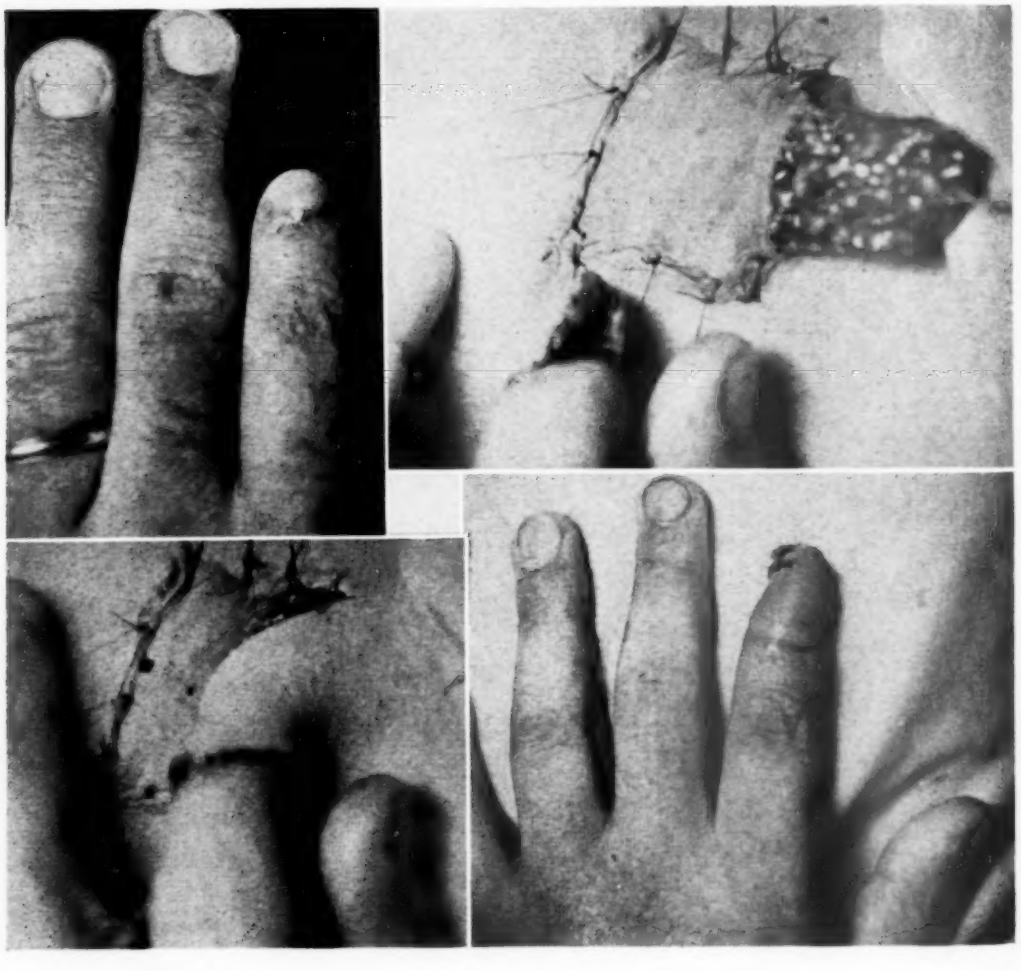


Fig. 7.—*A*, Hand of a young man with previous amputation of distal phalanx. Has good palmar touch pad rolled back over stump. Unable to reach certain keys in playing the piano professionally.

***B*, Palmar skin with normal sensation has been rolled forward. A bone graft has been pegged into middle phalanx in fifteen degrees of flexion.**

***C*, The dorsal and lateral defects are immediately wrapped in a pedicle flap from the abdomen. A split graft has been applied to donor defect.**

***D*, Flap has been detached sixteen days later. Resulting finger is a full 2 cm. longer. Patient states he is now able to play the piano easily, once more. A pedicle flap at the time of the original injury might have saved bone grafting, and preserved joint motion.**

Fortunately, immediate bone grafting is rarely needed as a primary procedure, and the simple digital flaps do not require either hospitalization or general anesthesia. The pedicles of these flaps may be divided after twelve to fourteen days. We have had no sloughs in these finger flaps although many have retrograde pedicles. The sutures, for even a simple closure of an amputated finger, are usually not removed for seven days. Thus, when finger flaps are used, the time away from work is not increased greatly over simple closure, and functional repair is much improved. Sensation has returned to a high degree in digital flap skin (Fig. 8).

Fig. 8.—Close-up of excellent match of cross-digital flap skin in tip of finger. This tip even showed excellent stereognosis postoperatively.

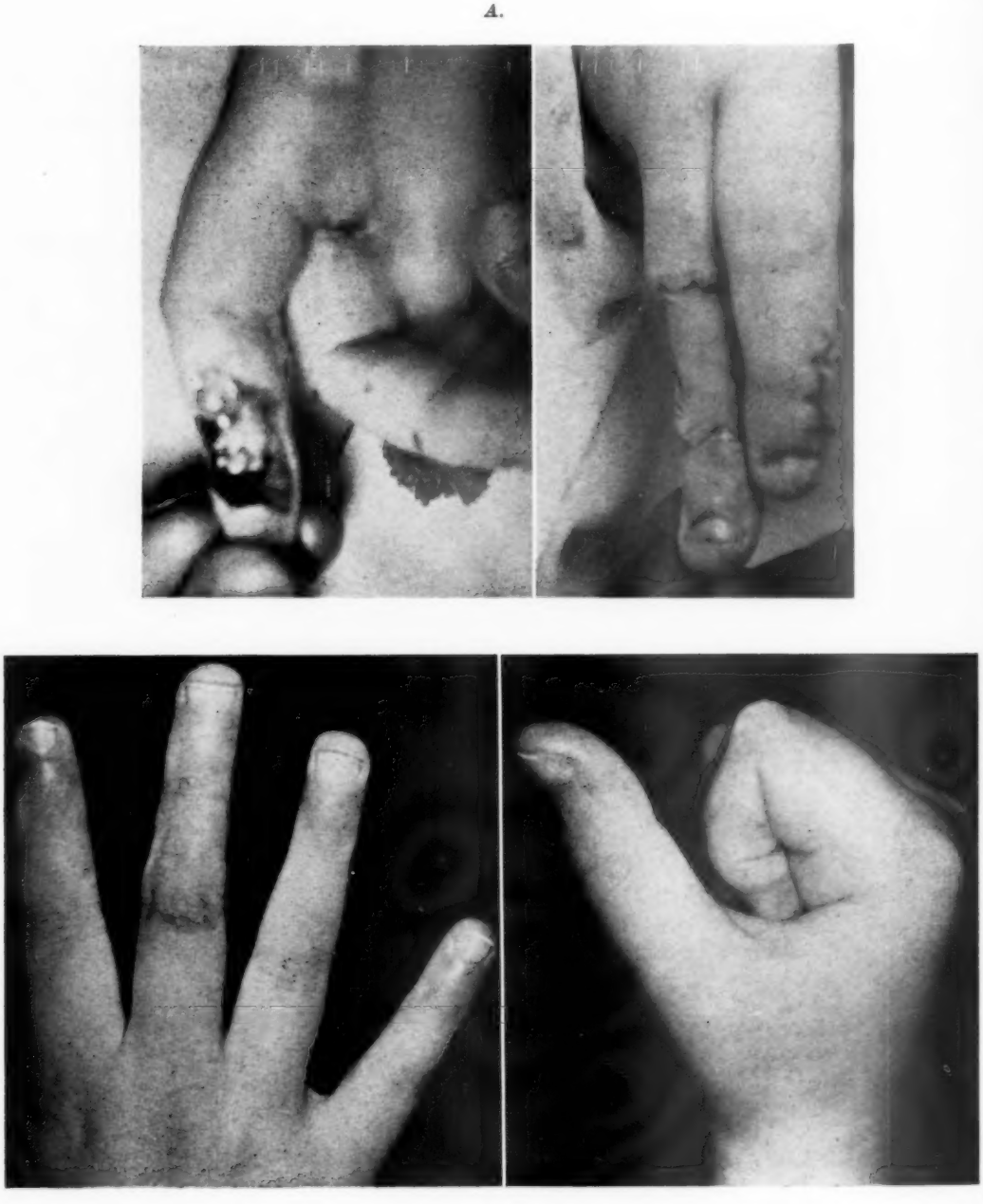
NERVE INJURY

Immediate nerve repair is quite important in reducing disability in the injured hand.[13] Trophic changes should be prevented, and are hard to reverse, at later dates. Digital nerves are, fortunately, purely sensory, and suture within the finger or hand will give consistently good results. Of twelve consecutive primary digital nerve sutures at The Johns Hopkins Hospital, only two failed to give excellent return of sensation. Autogenous nerve grafting of these sensory nerves is an excellent method to overcome gross gaps in nerves, but is best used as a clean secondary procedure. We have preferred to use the sural nerve as a graft. Next to furnishing good surface covering, we feel that nerve repair should receive earliest attention, as joints stiffen rapidly in anesthetic fingers. Only the nerve sheath is sutured in these anastomoses, and tantalum foil is not used around neural suture lines.

TENDON INJURY

Tendons should be repaired as emergencies, only if the wounds are very clean, and if the time elapsed, since injury, is very brief.[12] We rarely repair tendons after a period of four hours from the time of injury.

It is well known that adhesions often bind a tendon anastomosis that lies within the fibrous digital sheath. This "no man's land" of tendon repair poses a difficult problem for emergency care.[8] Two possibilities exist for



A. *B.* *C.*

Fig. 9.—*A*, Milk bottle avulsion of index finger has removed section of flexor profundus tendon along with full-thickness skin defect. The profundus has been lengthened at the wrist, and advanced into the distal phalanx. An immediate cross-digital flap has been used to cover the tendon and a small split graft may be seen on the dorsum of the donor long finger. The wrist and finger were then dressed in flexion.

B, Ten weeks after operation the patient has full extension of all fingers and minimal deformity at the site of the split graft.

C, The same patient has full flexion of the index with moderate return of sensation in less than three months following surgery.

immediate treatment: If the profundus tendon is divided in the region of the distal interphalangeal joint, the proximal stump may be simply advanced and attached into the bone of the distal phalanx. If the division is in the region of the proximal interphalangeal joint, it is often helpful to first lengthen the profundus tendon just above the wrist. This will gain enough length to advance the proximal stump once more for insertion into the distal phalanx (Fig. 9, *A*, *B*, and *C*). Such a maneuver offers the advantage of avoiding a suture line within the fibrous tunnel, and still preserves the vascular mesotenon and lumbrical muscle function of the finger. Lumbrical action to the finger will be weakened if this advancement is excessive (more than 2 cm.). Where

A.

B.

Fig. 10.—*A* and *B*, Excellent flexion and extension in a young woman only eight weeks after division of the flexor sublimis and profundus tendons of the little finger over the proximal phalanx. An immediate palmaris graft was inserted, so that no suture line lay within the fibrous digital sheath.

the profundus tendon is divided near or proximal to the center of the middle phalanx, it is, perhaps, best to merely close the wound and carry out secondary grafting as a clean procedure after several weeks. However, in the very clean injury, which involves only one or two fingers, immediate tendon grafting may be feasible. In a rather small series (eight) of such cases, we have had our very best results (Fig. 10, *A* and *B*). It must be emphasized, however, that the patients should be carefully selected. Good assistance and good anes-

A.

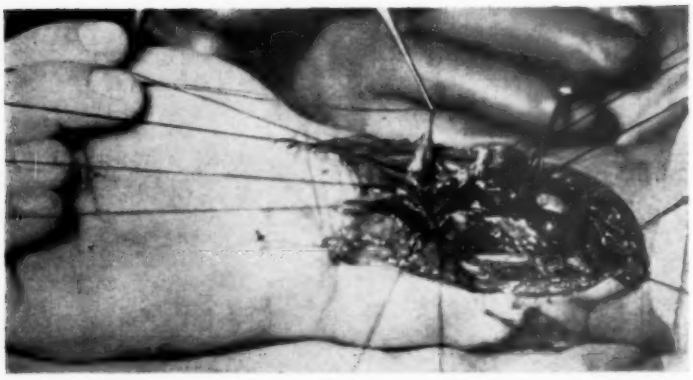


Fig. 11, *A*.—J. C. 560923. Hatchet injury in boy of 14 years. All flexor tendons to fingers and wrist divided. Median and ulnar nerves severed. Ulnar artery and vein divided. Immediate suture of all tendons and nerves carried out.

C.

D.

Fig. 11, *C* and *D*.—This hand enjoys balance and full flexion and extension only three and one-half months after the original injury.

B.

Fig. 11, *B.*—Sublimus tendons are being detached from their insertions. They are each split and threaded through the lumbrical tunnels as suggested by Bunnell. One slip has been used to give opposition to thumb. The split sublimis slips are attached to the extensor hood on both sides of each finger. The tension is adjusted so as to produce fifty degrees of metacarpophalangeal flexion and slight extension of the interphalangeal joints.

E.

Fig. 11, *E.*—Markings indicate the extent of sensory regeneration of median and ulnar nerves. In less than one and one-half years, sensation has returned except to three distal finger tips. Patient is using hand to run a printing press.

thesia should be available. Primary grafting is not a procedure to be carried out in the middle of the night, on the intoxicated patient, with little assistance, with poor anesthesia, or after a hard day's work.

EARLY HAND BALANCE

It is not within the scope of this paper to consider the many ramifications of late hand repair. Yet, it should be emphasized that early emergency surgery should not be started on the injured hand without a thorough understanding of the needs of later repair. Otherwise valuable tissue may be débrided, sublimis tendons may be discarded that are needed for later grafting, nerves may be lost in scar, making their secondary repair difficult, and granulating beds may be allowed to develop with resultant stiffening and fibrosis.

Within recent years we have felt that early substitution of motor power is indicated in cases of paralysis of the intrinsic muscles. This is particularly true where nerve injury has occurred in the upper forearm or arm. Immediate nerve repair is carried out, of course, but the regenerating nerve has a long course to cover, many of the motor fibers will find their way, by chance, into sensory channels, and months of disuse leaves small hand muscles atrophic and shortened. Galvanic stimulation has not been of great practical value to us in attempting to keep these small muscles in good condition over many months. As a result, high median and ulnar nerve injuries show only partial motor return, even when repaired ideally.

If the sublimis tendons are intact or have been repaired at the time of initial surgery, they may be used to substitute for lumbricals, interossei, thumb opponens, adductor, or any combination of these. A variety of useful transfers have been described repeatedly, and it is our contention that such transfers are best carried out after primary healing, but within a few weeks of initial injury. Only in this manner can the hand with small muscle paralysis be kept "in balance." Metacarpophalangeal joints will then remain flexible during nerve regeneration, and the thumb will not go into adduction contracture. In fact, these early transfers serve as excellent "built-in" elastic splints and furnish added strength, even in the event that motor components of nerve regeneration prove to be effective (Fig. 11, *A*, *B*, *C*, *D*, and *E*).

SUMMARY

The kinetic nature of the hand places a heavy premium on early return to motion. Even clean hand wounds, if left open, will lead to granulation tissue, fibrosis, adhesions, contracture, and joint stiffening. Early surface repair, with appropriate grafts and flaps, will prevent most of these "deformities, bred of caution." Newer antibiotics, copious irrigations, and careful débridement have made possible more definitive early surgery. This early surgery, in turn, makes possible better ultimate results with less pain and morbidity to the patient.

An integrated understanding of the use and construction of the hand is an essential to the selection of the procedure of choice.

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Appraisal of Progress in Surgical Therapy

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APPRAISAL OF RESECTION OF THE RECTOSIGMOID FOR CANCER

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CONTROVERSY has arisen over the problem of what is adequate surgical treatment of cancer of the rectosigmoid colon and rectum. Statistics have attempted to prove that one method is superior to others. We all know that conclusions from statistics are worthless unless they are gathered together and carefully scrutinized and analyzed by a competent and honest investigator.

Instruments of various sorts have been devised to overcome technical difficulties. Many forms of preoperative preparation have attempted to lower the morbidity and mortality, no matter what technical measures were pursued.

Approximately forty years ago, Sir Ernest Miles introduced the combined abdominoperineal resection of the rectum and of the rectosigmoid. The operative procedure was based on a careful study of the spread of the malignant tumor from the primary site. The operation has been widely accepted and has offered the most radical procedure and the greatest opportunity for cure of this malignant lesion.

The report of the infrequency of spread of carcinoma of the rectum or of the rectosigmoid to the lymph nodes distal to the tumor site by Westhues in 1934[1] and the confirmation of this work by Coller[2] and by David and Gilchrist[3] at a somewhat later time brought forth a revival of old operative procedures designed to preserve normal sphincteric action in the treatment of carcinoma of the rectum and of the rectosigmoid. Anterior resection of the rectosigmoid has been perfected by Wangensteen and Dixon, and the chief proponents of the operation of posterior resection have been Babcock and Bacon.

There are many descriptions in the literature as to what is the exact location of the rectosigmoid, there being no unanimity of opinion. Some authors stated that the site of the reflection of the peritoneum over bladder in the male and over the vagina in the female marks the position of the rectosigmoid, while others place the site of the "peritoneal reflection" laterally to the pelvic wall at the point where the mesosigmoid ceases to exist.

There is also considerable variation in the literature as to the distance of the rectosigmoid from the anal margin as measured or observed sigmoidoscopically. This is reported as being from 9 to 15 cm. Recently, Garlock and his

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associates[4] have measured the distance from the anal margin to the rectosigmoid at operation, employing calibrated rectal bougies, and they noted that there is considerable difference in various types of bodily build in this distance from the anal margin to the rectosigmoid. In the average individual it is observed to be between 9 and 14 cm.; in the obese individual this distance is much shorter; and conversely, tall lanky individuals may present a deep pelvis with a greater measurable distance from the anus to the rectosigmoid. We have attempted to correlate these observations in the operating rooms and consider the rectosigmoid to be located at the point where the mesosigmoid ceases to exist, where the peritoneum is reflected from the lateral walls of the sigmoid onto the pelvis and becomes merged with the pelvic peritoneum. This is usually at the level of the second segment of the sacrum. As alluded to previously, the location of the tumor process is of great importance, for it has been demonstrated that in the absence of involvement of contiguous viscera, the only deterrent to anterior resection should be the opportunity to realize sufficient length distal to the tumor site to be safely away from the possibility of distal spread. This has been based on a careful study of the lymphatics of the rectosigmoid and spread of tumor from the primary site along these channels. Westhues reported only one instance of spread to lymph nodes distal to the tumor site in seventy-four cases carefully studied. Cripps[5] in 1912 stated that the most successful cases are those in which operations were performed with a margin of one-half inch below the primary tumor. Cole[6] in 1913 noticed no instances of permeation microscopically beyond the edge of the growth in nineteen cases. Dukes[7] and others have been impressed with the limited extent of the intramural spread. Quer,[8] in a thorough study of ninety-one cases of carcinoma of the rectosigmoid, found only one instance of retrograde spread beyond 1.5 cm., and in eighty-six patients there was no retrograde spread at all. His conclusion was that in other than far-advanced tumors, Broders' Grade 3 or 4, a margin of 3 cm. of grossly uninvolved wall below the lowest palpable or grossly visible edge of the carcinoma is sufficient to make the operation adequate from the standpoint of retrograde intramural spread.

In contrast to the infrequent progression of tumor from the primary site distally, it has been observed that there may be considerable spread proximal to the primary site. Gabriel,[9] Gilchrist and David,[10] and Coller[11] have described the usual course of spread to be from the lesion to the pararectal nodes and from the pararectal nodes to the mesocolic nodes, and thence to higher para-aortic nodes. They have also demonstrated that an involved node usually prevents further spread until the node itself is replaced by metastatic tumor. In addition, these three groups of observers noted that there is occasional involvement of nodes just below the left colic artery without intermediate node involvement and, similarly, involvement of the mesocolic glands without involvement of the pararectal glands. Gilchrist and David examined eleven patients with incidental illnesses during the immediate postoperative period following abdominoperineal resections for carcinoma. Four of these patients showed metastases in nodes two inches above the upper limit of resection with any evidence of tumor in

proximal glands or in the liver. It becomes evident that the widest possible resection of the upper mesocolon should be carried out in all cases of carcinoma of the rectum and the rectosigmoid.

Excellent surgical, anatomic studies have been undertaken, particularly in the last two decades, which demonstrate the safety of ligation of the inferior mesenteric artery. Marginal vessels in most cases communicate freely with the middle colic and the left colic systems, obviating any question of adequate vascularization of the distal colon at the area of resection. The blood supply of the rectal stump in executing the anterior resection operation is almost always adequate with free anastomosis between the internal iliac system and through the middle and inferior hemorrhoidal vessels. It would seem that the limit of resection for carcinoma of the rectosigmoid need not be related to limitation of blood supply.

With this background we reserve the procedure of anterior resection of the rectosigmoid for those carcinomas just above the level of the reflection of the mesocolon to the lateral pelvic peritoneum, provided that there is no involvement of juxtaposed tissue and that it is possible to obtain 5 cm. in length below the lowest visible or palpable tumor at the primary site. The operation of anterior resection of the rectosigmoid is well known, but the following data are worthy of emphasis. The superior hemorrhoidal or inferior mesenteric arteries are ligated, thus permitting removal of a longer segment of the lower sigmoid and assuring removal of all of the lymph nodes of the lower mesosigmoid. The rectum is bluntly dissected to the tip of the coccyx, much as is done in the combined abdominoperineal resection. The ureter is isolated and retracted laterally on each side, and lateral and anterior peritoneal flaps are prepared. For carcinomas at the rectosigmoid or just above the peritoneal reflection, it is not necessary to ligate the middle hemorrhoidal vessels, for a wide enough margin can be resected without this maneuver. The anastomosis should be accomplished with care without tension. This is most accurately done with the employment of an open type of procedure, using fine silk sutures for the outer layer and fine catgut for the mucosa. The pelvic peritoneum is approximated above the anastomosis, and drains are brought out of the lower angle of the operative wound from the area of the anastomosis. We believe that proximal decompression makes for a smoother convalescence and a more rapid healing of the suture line, whether this be by means of a transverse loop colostomy or by means of a tube cecostomy. These may be closed by the third week when firm healing and patency of the primary anastomosis are demonstrated.

In Garlock's excellent study of the operation of anterior resection of the colon, he found that when operations were limited to the rectosigmoid, as described, there was a recurrence rate at the suture line of 4 per cent, as compared to a recurrence rate of 10 per cent at five to six inches, 40 per cent at four to five inches, and 27 per cent at three to four inches. Recurrences within the pelvis behaved comparably, increasing in frequency as one decreased the distance the tumor existed prior to resection from the anal skin margin.

In a series of fifty-five cases of primary resection and end-to-end anastomosis for carcinoma of the colon, W. H. Cole[12] found that there were nine recurrences

over the period of observation and that six of these were present at the suture line. In explaining this problem of recurrence at the suture line, he feels that this is related to the implantation of live cancer cells displaced from the primary site at the time of operative manipulation or desquamated into the lumen of the bowel before resection. If inadequate resection of the bowel wall were the explanation, one would expect to find many more instances of recurrence at the site of the colostomy in the combined abdominoperineal resection, and this is rare. To obviate this problem, it is suggested that tape ligatures be placed around the bowel 3 cm. above and below the tumor before any manipulation is carried out. As the diseased bowel is being resected, clamps are applied to the colon proximally and distally, and each segment is thoroughly irrigated with saline solution or distilled water. After the irrigation, a small segment is resected from either end to eliminate the possibility of trapping other cells at the site of the application of the clamps.

For invasive carcinoma at or below the pelvic peritoneum, a combined abdominoperineal resection is carried out with mobilization of the rectum including all pararectal tissue, extensive mobilization of the splenic flexure and the descending colon, high ligation of the inferior mesenteric artery as well as the inferior mesenteric vein with removal of all of the mesentery lateral to the marginal vessels, creation of a terminal colostomy at the juncture of the descending colon and the sigmoid or higher if there is any question of viability, and wide perineal and levator excision.

The percentage of patients submitted to combined abdominoperineal resection has increased during the last ten years, and it has been possible to remove 85 per cent of the rectal lesions. In spite of this greater application of the procedure to the lesion, the mortality has gradually been reduced and now remains under 7 per cent. Complications following the procedure have likewise diminished, with better preparation with an improved operative procedure and with the use of antibiotics and improved postoperative care. Urinary complications still remain a prominent feature during the postoperative period. As the percentage of resected cases has increased with the inclusion of unfavorable cases, particularly the 44 per cent of patients who have liver metastases, satisfactory results in patients followed five years or more have decreased so far as five-year percentage figures are concerned. Without question, with the wider application of the procedure of combined abdominoperineal resection, a greater salvage of patients has resulted, and much greater comfort has been produced in those patients who were incurable from the start, without increasing the mortality. From this experience we believe that the combined abdominoperineal resection is the operative procedure of choice in all patients who have carcinoma at the pelvic peritoneal reflection, of the rectum, and of the anus.

It is conceded by many that the Lockhart-Mummery procedure is applicable and valuable in elderly, poor-risk patients, particularly where the growth is situated below the level of the peritoneal reflection. The operation, to be carried out successfully, must be predicated upon the presence of a redundant sigmoid colon.

CONCLUSIONS

A tumor process located in the rectosigmoid in general should be treated by combined abdominoperineal resection if the process is located at or below the reflection of the mesosigmoid onto the pelvic peritoneum. If there is no involvement of contiguous viscera, if it is possible to realize 5 cm. in length below the lowest grossly palpable tumor, and if the tumor process is located above the rectosigmoid, there is adequate laboratory and clinical evidence to support the choice of the anterior resection operation.

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Book Reviews

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers as space permits.

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